# FDA Executive Summary
# BioMimetic's Augment Bone Graft

# Orthopedic and Rehabilitation Devices Panel

# May 12, 2011

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## INTRODUCTION

The subject of this Executive Summary is **BioMimetic's Augment™ Bone Graft** premarket approval (PMA) application, P100006. Augment is a combination product (device and biologic drug) consisting of Recombinant PDGF-BB (becaplermin) packaged together with β-TCP in the surgical fusion treatment of foot and ankle bone defects of all causes use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular, and calcaneocuboid fusions. This application has been reviewed by staff in the Center for Devices and Radiological Health (CDRH) and Center for Drug Evaluation and Research of the Food and Drug Administration (FDA). Your time and effort in the review of this application is greatly appreciated.

### Rationale for Presentation to the Panel

The FDA presents this PMA to the Orthopedic and Rehabilitation Devices Advisory Panel for the following reasons:

- The Augment™ Bone Graft is the first combination product utilizing rh-PDGF-BB to be indicated for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular, and calcaneocuboid fusions.
- FDA has ongoing concerns with the possible toxicity of this product as well as the ability of the studies to date to demonstrate reasonable safety and effectiveness and will describe these concerns in this summary.

### FDA Questions to the Panel

The FDA would like the Panel to provide responses to a series of questions regarding the safety and effectiveness data contained in P100006. These questions are located in the "FDA Panel Questions" section of the Panel package.

## BACKGROUND INFORMATION

### Applicant Name and Address

BioMimetic Therapeutics, Inc.
389-A Nichol Mill Lane
Franklin, Tennessee 37067

### Indications for Use

The following Indications for Use were specified in the IDE clinical study for Augment™ Bone Graft G050118:

"The intended use of the device is as an alternative bone grafting substitute to autologous bone graft in applications to facilitate fusion in the ankle and foot without necessitating an additional invasive procedure to harvest the graft."

The following Indications for Use are proposed by the sponsor in the PMA:

“The intended use of Augment™ Bone Graft is indicated for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular, and calcaneocuboid fusions."

### Contraindications

The sponsor proposes that the use of Augment™ Bone Graft be contraindicated in the following cases:

- For patients with a known hypersensitivity to recombinant PDGF-BB.
- In the vicinity of a resected or extant tumor or any active systemic malignancy or patients undergoing treatment for a malignancy.
- In patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- In pregnant women. The potential effects of rh-PDGF-BB on the human fetus have not been evaluated.
- In patients with an active infection at the operative site.

### Warnings

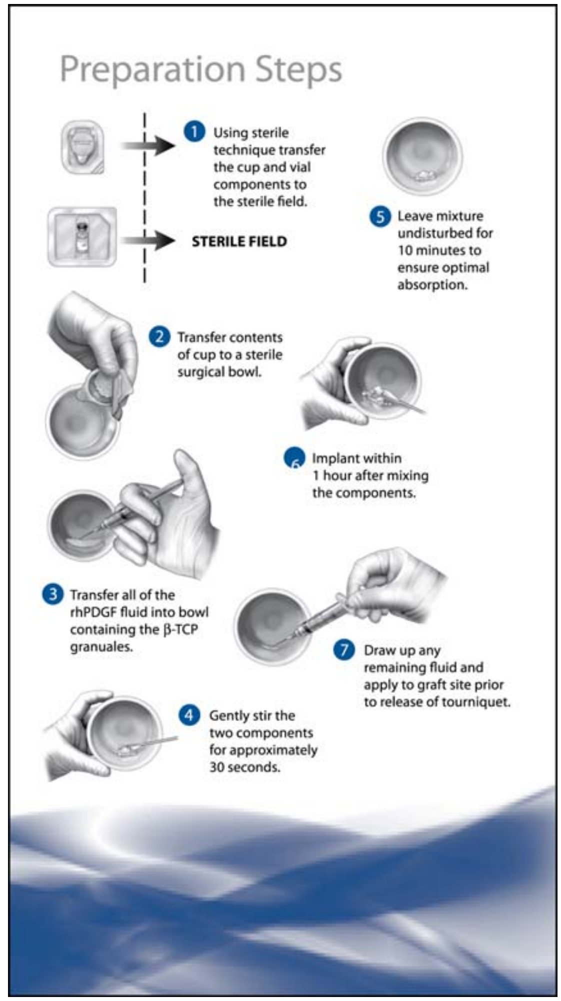
The sponsor proposes that the following warnings be included in the labeling for Augment™ Bone Graft:

- Women of childbearing potential should be advised that the influence of rh-PDGF-BB on fetal development has not been assessed.
- The effect of maternal antibodies to rh-PDGF-BB might be present for several months following device implantation.
- The safety and effectiveness in nursing mothers has not been established. It is not known if PDGF-BB is excreted in human milk. Women of childbearing potential should be advised not to become pregnant for one year following treatment.
- Use of Augment™ Bone Graft has not been established in anatomical locations other than the foot or ankle, used in surgical techniques other than open surgical approaches, or combined with autogenous bone or other bone grafting materials.
- Augment™ Bone Graft does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.

### Device Description

The Augment™ Bone Graft is a combination product consisting of 2 components: a therapeutic protein becaplermin or recombinant human platelet-derived growth factor BB (rh-PDGF-BB) in a solution of 0.3 mg/mL in 20mM USP sodium acetate buffer and a bone matrix of beta tricalcium phosphate (β-TCP) in granule particulate form.

The components of Augment™ Bone Graft are packaged separately and mixed just prior to implantation by a surgeon. Augment™ Bone Graft must be stored at refrigerated temperatures (2-8°C). The product is manufactured by Pyramid Laboratories (Costa Mesa, Ca). The rh-PDGF-BB is supplied as 1.5 ml or 3 ml/vial of a 0.3 mg/ml rh-PDGF-BB solution. The β -TCP is supplied in 1.5, 3, 6, and 9 cc. Both the rh-PDGF-BB and β -TCP will be supplied in one-to-one ratio as 1.5, 3, 6, and 9 ml (or cc) quantities per drug product (DP) package.


<u>Recombinant Human Platelet Derived Growth Factor</u>
Recombinant human platelet-derived growth factor chain B (rh-PDGF-BB) protein is a member of PDGF-BB family of growth factors. In total, there are four PDGF-BB chains, A, B, C, and D2. The four PDGF-BB chains dimerize to form five different isoforms: PDGF-BB-AA, PDGF-BB, PDGF-BB-CC, PDGF-BB-DD, and PDGF-BB-AB. The dimerization is facilitated by three intra-molecular and two inter-molecular disulfide bonds. The resulting structure forms a knot-like structure and hence, the PDGF-BB family belongs structurally to the cystine knot motif containing family of growth factors. The rh-PDGF-BB bulk material is a heterogeneous protein. Recombinant human PDGF-BB monomer is 109 amino acids long and the molecular weight of the dimer is 24.5 kDa.

The rh-PDGF-BB is chemotactic for fibroblasts, neutrophils, and monocytes, cell types important for the early phases of tissue repair. The rh-PDGF-BB is mitogenic for fibroblast, osteoblasts, chondrocytes, and mesenchymal stem cells which are important for later stage tissue formation. The rh-PDGF-BB functions as a chemo-attractant and mitogen for cells involved in wound healing and through its promotion of angiogenesis at the site of healing.

Beta Tricalcium Phosphate
The β -TCP acts as bone void filler to prevent soft tissue from collapsing into the void. When the β -TCP is placed near a viable host bone, it acts as scaffold for new bone growth (osteoconductive). The particle size ranges from approximately 1000 to 2000 microns in diameter.

Directions for Use
At the time of surgery the B-TCP granules and the vial(s) containing the rh-PDGF-BB solution are mixed for 30 seconds using a spatula, curette or similar instrument. The mixture should be left undisturbed for 10 minutes before being implanted to ensure optimal saturation of the B-TCP particles. Please note that both components have been previously approved by the FDA for other specified indications. The rh-PDGF-BB is a licensed product manufactured by Novartis and is currently used as a component in Regranex® and GEM 21S. The β -TCP is a registered device called OsteoMimetic. In addition, GEM 21S®, a device composed of chemically identical materials are approved for use in both the U.S. (PMA #040013) and Canada (MDL #71464) for the treatment of bony defects associated with periodontal applications.

**Regulatory History**

The Augment™ rh-PDGF-BB Bone Graft is not marketed in the United States or any foreign country other than in Canada since November 2009, and has only been used in IDE studies in the United States. As previously stated, the rh-PDGF-BB and the B-TCP have been marketed in the United States as part of another pre-market approval (PMA). The rh-PDGF-BB has been marketed in the United States as a biological license application (BLA).

- P040013 - GEM 21S – rh PDGF-BB and B-TCP was approved to treat the following periodontal related defects that include intrabony periodontal defects; furcation periodontal defects; and, gingival recession associated with periodontal defects.
- http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078383.htm
- BLA# 961422, BLA#103691 - rh PDGF-BB was the active ingredient of *Regranex*® gel approved for the indications for the treatment of lower extremities diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. Regranex Gel is indicated as an adjunct to, and not a substitute for, good ulcer care practices. See attached Regranex® labeling.
    - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107697.pdf
    - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm086100.pdf
- See the following links regarding communications about an ongoing safety review of Regranex® (becaplermin). FDA/CDER was informed of information obtained from epidemiologic evaluations of the use of *Regranex* and a possible link to increased mortality from existing cancer. In March 2008, the FDA issued an Early Communication concerning a possible link between multiple uses of Regranex and an increase in mortality from pre-existing cancers. This was specifically true for patients who had had three or more dose regimens compared to those who had not used Regranex. There was no reported increase in the incidence of new cancers. Physicians were warned in a

labeling change not to prescribe three or more dose regimens in patients with pre-existing cancer.

- http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm072121.htm
- http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm072148.htm
- http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm121631.htm
- http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048471.htm

Additional information regarding Regranex® gel and its active ingredient of rh PDGF-BB is as follows:

REGRANEX® (becaplermin) BLA# 103691
Becaplermin bulk drug substance is the active ingredient of *Regranex®* gel, which is approved for treatment of diabetic ulcers. *Regranex* gel received marketing approvals in the United States (December 1997), and OUS in 1998 and 1999. *Regranex* gel has not been withdrawn from these markets for any reason. *Regranex* is indicated for the chronic treatment of slowly healing diabetic, neuropathic cutaneous wounds in the lower extremities and can be used daily for up to 20 weeks. FDA/CDER was informed of information obtained from epidemiologic evaluations of the use of *Regranex* and on March 27, 2008, FDA issued an Early Communication (EC) regarding the use of *Regranex* and a possible link to increased mortality from existing cancer.[1] *Regranex* contains the same rh-PDGF-BB as the *Augment* product. In addition, the EC stated that FDA was reviewing a post-marketing, insurance database study and would issue additional information once their review was completed. In July 2008, FDA required that the label of *Regranex* be modified to include a warning. The black box warning reads as follows:

**Warning: Increase Rate of Mortality Secondary to Malignancy**

**An increase rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a postmarketing retrospective cohort study. REGRANEX Gel should only be used when the benefits can be expected to outweigh the risks. REGRANEX Gel should be used with caution in patients with known malignancy.**

Upon review of the EC, Biomimetic contacted members of both CDRH and CDER to discuss the information. Based on discussions with FDA, Biomimetic is performing additional pre-clinical testing to further research whether there is any potential effect from PDGF-BB regarding increased mortality from existing cancers. The proposed studies are intended to assess the potential for rh-PDGF-BB to induce developmental toxicity, long-term carcinogenicity and enhance tumor progression. We will be asking the panel if these studies or additional studies are needed prior to marketing or any additional study is needed as part of a post approval study.

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[1] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm072121.htm

Dosing Comparison between Regranex and Compared to Augment
The clinical utility of rh-PDGF-BB to stimulate tissue repair has been evaluated with Regranex®, containing 0.01% rh-PDGF-BB in a gel formulation in a BLA, for the treatment of non-healing lower extremity diabetic ulcers. Due to slow healing of cutaneous ulcers, the typical administration is 112 to 140 repeat doses over 16-20 weeks. Typical ulcer sizes average approximately 5 $cm^2$ (up to a maximum of 100 $cm^2$), with treatment of 16-20 weeks duration.

One 15 ml tube of 0.01% Regranex corresponds to a content of rh-PDGF-BB of 1.5 mg. Three (3) tubes for repeated dosing contain a total of 4.5 mg of rh-PDGF-BB which - on average - would be used over a period of 13 weeks. For the typical administration over 16-20 weeks, the total dosing of rh-PDGF-BB corresponds to 5.5 to 6.9 mg. Based on a Regranex dose of 7 μg/$cm^2$ ulcer and a maximum ulcer size of 100 $cm^2$ the maximum exposure to Regranex for 20 weeks would be 98 mg.

In comparison, the typical administration of Augment Bone Graft is 6 cc of β-TCP and 6 mL of 0.3 mg/mL rh-PDGF-BB corresponding to a one time administration of 1.8 mg of rh-PDGF-BB. The maximum dose administered in the pivotal clinical trial BMTI-2006-01 was 9 cc of β-TCP and 9 mL of 0.3 mg/mL rh-PDGF-BB corresponding to a one time administration of 2.7 mg of rh-PDGF-BB. Table 1 shows the comparison in detail.

**Table 1 Dosing comparison of rh-PDGF-BB in Augment™ and Regranex®**

| Product | Augment™ Bone Graft | Regranex® | Ratio Regranex/Augment |
|---|---|---|---|
| Administration frequency | One time | Repeated over 13-20 week | |
| Typical clinical dose of rh-PDGF-BB | 1.8 mg | 4.5 - 6.9 mg | 2.5 - 3.8 |
| Maximum clinical dose | 2.7 mg | 98 mg | 36 |

## PRE-CLINICAL EVALUATION OF AUGMENT

### Biocompatibility Testing Summary

The sponsor’s device, Augment™ Bone Graft, is composed of β-Tricalcium Phosphate (β-TCP) and rh-PDGF-BB (Becaplermin), as is described elsewhere.

Safety Evaluations – Biocompatibility
Medical devices permanently implanted in bone or soft tissues are recommended via ISO 10993-1 to have the following evaluations:

- Cytotoxicity
- Sensitization
- Genotoxicity
- Implantation
- Chronic toxicity
- Carcinogenicity

- Reproductive / Developmental

The sponsor evaluated the product, as constituted with different matrices in pre-clinical evaluations to address safety. The results indicate that the combination product is biocompatible with some indications of mild to moderate irritancy seen in the implantation and cytotoxicity evaluations. The sponsor did not conduct a classic chronic toxicity evaluation; however, they did perform animal proof-of-concept evaluations which provided information to meet the chronic toxicity type of assessment requirements. Animal model evaluations included assessments in rodent, rabbit, and canine models, and the sponsor concluded that the product was demonstrated to be safe in these assessments.

Carcinogenicity evaluations for permanently implanted medical devices in tissue/bone are typically recommended if genotoxicity evaluations indicate a concern, or if the chemical components of the device are considered to have potential carcinogenic character. Drug products are typically evaluated for carcinogenicity in 2 rodent-based assessments, e.g., the standard 2 year rodent assessment and/or rodent-based transgenic model evaluations. Reproductive toxicology evaluation is required, for devices, as indicated and needed. In the case of combination products such as Augment™ Bone Graft, FDA has considered that carcinogenicity evaluation, in addition to genotoxicity evaluation, is needed and that reproductive toxicologic analysis should also be conducted. The sponsor has conducted evaluations for carcinogenicity and reproductive toxicity and concluded that the product was determined to be safe in those assessments. However, FDA has requested additional study of the product for both safety concerns. FDA will be asking questions related to these studies and any unresolved carcinogenic, tetrogenic, and/or immunological issues that may need further pre-clinical, clinical or post-market testing.

**Reproductive / Developmental**

The use of a therapeutic protein, or drug, during pregnancy could have adverse effects on the developing fetus. FDA has considered that reproductive toxicology evaluation for this combination product consisting of a device and a biological drug is warranted and is necessary. The sponsor has conducted a standard reproductive toxicology evaluation. This evaluation satisfies the standard reproductive toxicology requirement for traditional implanted medical devices. However, a combination product, using a therapeutic protein component, could elicit antibody formation. Antibodies formed to the implanted rh-PDGF-BB protein could cross react with endogenous PDGF-BB protein in the patient's body. If the antibodies are of a neutralizing character, they could interfere with normal PDGF-BB signalling within the body. If the neutralizing antibodies were to cross the placental barrier in a pregnant female, they could interfere with the role of PDGF-BB during the growth and development of the fetus with severe adverse consequences. The antibodies, in a worst case scenario, could effectively "knock-out" the gene (or in this case, gene-product) for the protein which could result in a dominant lethal effect.

In response, the sponsor has proposed to conduct a reproductive toxicology assessment in rodents using the one known neutralizing antibody to PDGF-BB, i.e., a commercially available goat anti-rh-PDGF-BB IgG antibody.

The sponsor has been working towards answering this question. They have known for some time that this is an issue to address. The sponsor was informed of this concern while the IDE was ongoing, although near the end of the study's progress. Continued discussion with the sponsor regarding their protocol is necessary. The sponsor indicates that they are at least 6-9 months away from initiating the evaluations based upon “CRO availability and R&D Systems schedule for antibody production.” The sponsor, in the meantime, “commits to initiate a strong effort to generate anti-rh-PDGF-BB antibodies in rabbits, as well as in rodents.” Until the approach to this assessment can be formalized between FDA and the sponsor, the product label will need to include a Boxed Warning for women of reproductive age and capabilities similar to that included in the rhBMP-2 product label.

### Pharmacology / Toxicology

Nonclinical studies were conducted addressing primary pharmacology, toxicokinetics, developmental toxicity and toxicity at multiple doses with rh-PDGF-BB alone or in combination with β-TCP. The sponsor’s nonclinical toxicity assessments of rh-PDGF-BB were designed to address concerns for systemic rh-PDGF-BB toxicity following a single clinical dose. A joint fusion study in dogs suggests that permanent local toxicity is not anticipated and the outcome should be similar to the standard care.

Primary Pharmacology
A joint fusion study in dogs treated with rh-PDGF-BB/β-TCP or autograft suggests that permanent local toxicity is not anticipated and the fusion outcome should be fairly similar to autograft.

Toxicokinetics
Sustained systemic exposure to high levels of rh-PDGF-BB is not anticipated with Augment™ Bone Graft Material. In rats, rh-PDGF-BB is rapidly mobilized to systemic circulation after intramuscular injection with β-TCP. The half-life of radioactivity in rats after intramuscular injection of $^{125}$I-rhPDGF-BB/B-TCP was 30 hours and only 0.5% of the dose was detected at the application site and 3% in the total carcass one week after dosing. Upon transfer to circulation rh-PDGF-BB is rapidly and extensively metabolized such that little whole rh-PDGF-BB is in urine or feces. In rats dosed intravenously with $^{125}$I-rhPDGF-BB the half-live was biphasic (0.04 and 7.5 hrs) with nearly the entire dose eliminated within 24 hours.

Toxicology
A two-week intramuscular repeat-dose toxicity study was conducted in rats with rh-PDGF-BB without β-TCP. Rats were dosed with rh-PDGF-BB next to the femur and metatarsus every other day for two weeks. Rh-PDGF-BB was well tolerated at doses up to 10 μg per injection site, which roughly equates to 3 times the maximal clinical dose (2,700 μg, 45 μg/kg body weight) based upon mg/kg body weight. Mild, but temporary, osteogenesis and fibroplasia of the cortical layer of the bone was observed near the injection site and the severity was slightly elevated in rats dosed with 10 μg of rh-PDGF-BB compared to control animals. Adverse affects were not observed other than temporary mild injection site swelling with inflammatory cell infiltration.

## CLINICAL STUDY DESCRIPTION

**This section summarizes the IDE clinical study protocol.**

## Introduction

Damage to articular cartilage in the foot and ankle by acute or chronic injury causes pain, limits function, and leads to osteoarthritis. Over the years, surgical fusion (arthrodesis) techniques have been developed to stop motion between damaged joints and effectively reduce pain and improve function. The primary goal of arthrodesis is to create a solid bony mass between opposing bones. To accomplish this, articular surfaces are denuded and materials, which fill in the space and accelerate bone growth, are used. These include autogenous bone graft, allogenic bone graft, and bone void fillers. The most common material used to accelerate union is autogenous bone graft. The success of autogenous bone graft in a large series of ankle arthrodeses is reported to be 72%. The major risk of arthrodesis is to create an ineffective fusion leading to non-union, delayed union, and pseudoarthrosis. Fusions techniques, especially in the ankle, are technically very demanding and operator sensitive. Close contact between fusion elements, avoidance of fixative methods, which promote distraction, and proper alignment are very important elements for success. Ankle fusions, in particular, often require a prolonged time for bony consolidation (greater than 1 year) and are associated with a high rate of non-union.[2]

## Purpose

The purpose of this clinical study, as stated in the IDE investigational G050118 was to evaluate the safety and effectiveness of the Augment™ rh-PDGF-BB Bone Graft for patients requiring ankle and hindfoot fusions for bony defects requiring surgical intervention. The ability for this device to provide successful fusion of an “all complement of joints” was assessed by CT at 24 weeks and compared to implantation of autogenous bone harvested either locally or from the iliac crest. The fusion site was stabilized with no more than 3 internal fixation screws, but without plate fixation or restriction on external supplementary screws or pins.

Safety was assessed by comparing the nature and frequency of adverse events during surgery and postoperatively between the two groups of patients. Subset analyses include 7 subgroups defined as pre-treatment signs and symptoms; treatment emergent adverse events (TEAE); “complications”; serious “complications”; infections related TEAE; and serious TEAE. In addition, serum studies for anti-rh-PDGF-BB antibodies were conducted. Safety events were not considered in the overall determination of study success and were provided only as post-hoc assessments. The primary efficacy objective was assessed by evaluating radiographic evidence of fusion success by CT at 24 weeks. An additional assessment of clinical success (function and pain) was collected secondarily (and analyzed post-hoc according to sponsor defined outcome measures per an FDA request for a combined endpoint as described further below).

## Study Design

The sponsor provided data from the pivotal multi-center, prospective, randomized, concurrently controlled, partially single-blinded[3], non-inferiority trial of the Augment™ rh-PDGF-BB Bone

[2] Lance EM, et .al.: Arthrodesis of the ankle joint, A follow-up study. Clin Ortho Related Res. 142:146, 1979.

[3] Treating clinical staff were not blinded; subjects were blinded until after surgery (subjects would have become un-blinded after surgery based upon presence or absence of a bone graft harvest surgical site).

Graft compared to ankle and hindfoot fusion using autogenous bone in patients with bony defects requiring surgical intervention as defined in the study inclusion/exclusion criteria outlined below. The study involved 435 randomized patients and 272 treated investigational and 142 treated controls at 38 U.S. and Canadian sites.

**Primary Study Endpoint / Success Criteria**

Individual patient success (i.e., overall success) was determined at 24 weeks and was defined as a single endpoint. A patient was considered a success if the following criteria regarding both safety and efficacy were met:

- Fusion defined as
  - CT evidence of greater than 50% osseous bridging
  - Involving a "full complement of joints"

[Note: FDA has requested that the sponsor validate the usage of this outcome method to determine fusion for both the IDE and the PMA but this has not yet been provided. FDA will ask a question relating to the validity of the study endpoints to the panel.
Fusion outcomes as defined above were used to indicate both radiographic and clinical success. The FDA current recommendation is that fusion should be defined as follows: plain radiographic evidence of three out of four bridged cortices, absence of joint articular lines, and no pain on clinical examination at the surgical site and/or with weight bearing (with the use of assist devices).

**Secondary Study Endpoints**

The secondary study endpoints were determined at 24 weeks and evaluated to compare the success rates of the individual safety and effectiveness endpoints, including operative measurements. Secondary endpoints included:

1.) Fusion success rate at 24 weeks (by an independent masked radiologist)
   - By CT: For a full complement of joints, success defined as greater than 50% osseous bridging of each joint for which fusion was attempted.
     i. If a patient had a secondary procedure, identified as use of bone stimulators or revision surgery, prior to that study visit, that patient was considered a failure.
   - By plain radiographs: Success defined as 3 of the 4 radiographic aspects (medial, lateral, anterior/superior, posterior/inferior) demonstrating osseous bridging with disappearance of the joint space at each treated joint.
     i. Each plane was classified as fused, not fused, or not evaluable.

2.) "Clinical success" defined as the combination of the following 2 endpoints
   a. Improved pain, as assessed on the VAS scale, with weightbearing compared to baseline
   b. No need for revision surgery

3.) A patient was declared a "composite success" if:
   - Surgical treatment was completed per protocol
   - Patient was declared to have union or evidence of progressive healing at week 24

- CT scans for the full complement of joints demonstrated osseous bridging assessed as at least 25% at week 24
- The patient experienced no SAEs of possible relation to study treatment by week 24
- The patient's VAS pain assessment was less than 20 mm at the graft harvest site at week 6 and after
- There was no need for secondary therapeutic intervention at or before week 24

4.) "Therapeutic failures" defined as
   - For non-union established at 36 weeks postoperative when the fracture/fusion site showed no visibly progressive signs of healing for a minimum of 3 months (no change of fracture callus)
   - For delayed unions established when insufficient fracture/fusion healing determined by radiographic assessment between 24 and 36 weeks

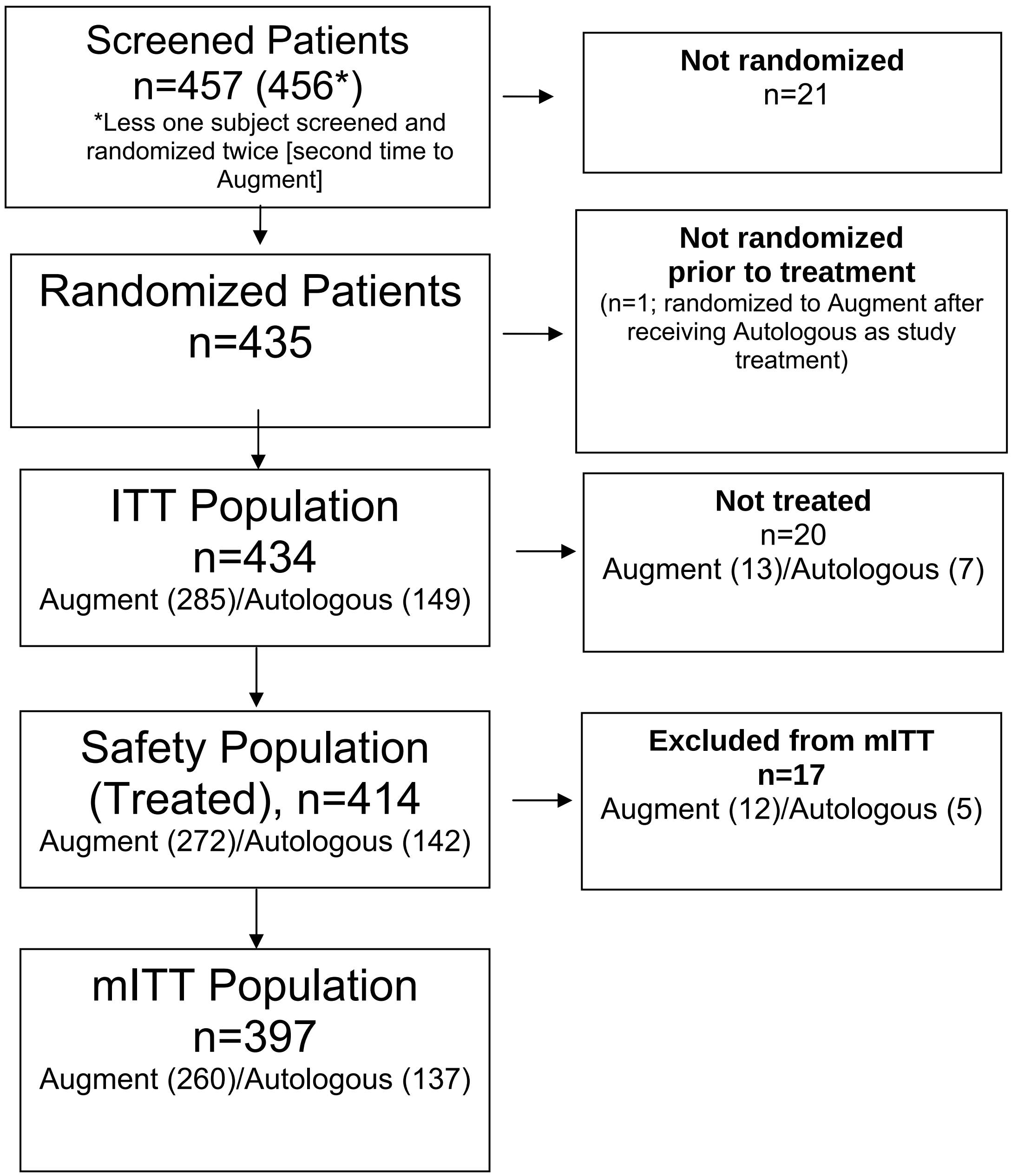
5.) Quality-of-life assessed using the following questionnaires
   a. SF-12
   b. FFI
   c. AOFAS Ankle-Hindfoot

6.) Pain assessments made on a VAS scale with regards to 3 components:
   a. Overall fusion site pain
   b. Pain on weight-bearing
   c. Pain at the graft harvest site (for patients in the autologous bone graft treatment group).

Protocol Study Success and Modifications

The study was considered a success if the Overall Success Rate for the device was determined to be non-inferior as compared to the Overall Success Rate for the control. The primary effectiveness endpoint of the trial was CT fusion rate at 24 weeks of the "full complement of joints" in the modified intent to treat population (mITT), defined as all randomized patients who were eligible, properly randomized, and received treatment according to the study protocol. The ITT population consists of all randomized patients, including intra-operative screen failures and non-treated patients, who were analyzed according to the treatment to which they were randomized and were used to support the analysis of the primary effectiveness endpoint. [N.B. As is described further below, the sponsor has modified the study protocol for the current PMA to use a mITT population - which will be described further and analyzed below.] Patients with secondary procedures (use of bone stimulators or revision surgeries for non-union and delayed union) were counted as CT fusion failures. See the figure below for the overall breakdown of the subject populations.

**Subject Populations**



**Inclusion/Exclusion Criteria**

| Table 2 – Inclusion Exclusion Criteria | |
|---|---|
| **Inclusion Criteria** | **Exclusion Criteria** |
| 1. The patient signed the IRB-approved Informed Consent Form specific to this study prior to enrollment.<br>2. The patient had a bone defect in the hindfoot or ankle requiring fusion using open surgical technique with supplemental bone graft/substitute, requiring one of the following procedures:<br>• Ankle joint fusion (tibiotalar fusion)<br>• Subtalar fusion<br>• Calcaneocuboid fusion<br>• Talonavicular fusion<br>• Triple arthrodesis (subtalar, talonavicular and calcaneocuboid joints)<br>• Double fusions (e.g., talonavicular and calcaneocuboid joints)<br>3. The fusion site was able to be rigidly stabilized with no more than 3 screws across the fusion site. Supplemental pins may have been used. Supplemental screws external to the fusion site(s) were also allowed. Plate fixation was not part of the study protocol and was excluded.<br>4. The patient was independent, ambulatory, and could comply with all post-operative evaluations and visits.<br>5. The patient was at least 18 years of age and considered to be skeletally mature. | 1. The patient had undergone previous surgery of the proposed fusion site.<br>2. The fusion site required plate fixation, more than 3 screws across the fusion site to achieve rigid fixation, or more than 3 kits (9 cc) of graft material.<br>3. There was radiographic evidence of bone cysts, segmental defects or growth plate fracture around the fusion site that may negatively impact bony fusion.<br>4. The patient currently had untreated malignant neoplasm(s) at the surgical site, or was currently undergoing radio- or chemotherapy.<br>5. The patient had a pre-existing sensory impairment (e.g., diabetes with baseline sensory impairment) which limited the ability to perform objective functional measurements and may have placed patients at risk for complications. For the purpose of this protocol, diabetics that were not sensitive to the 5.07 monofilament (Semmes-Weinstein) were to be excluded.<br>6. The patient had a metabolic disorder known to adversely affect the skeleton, other than primary osteoporosis or diabetes (e.g., renal osteodystrophy or hypercalcemia).<br>7. The patient used chronic medications known to affect the skeleton (e.g., glucocorticoid usage > 10 mg/day). Non-steroidal anti-inflammatory drug (NSAID) use was excluded during the first 6 weeks post-operatively.<br>8. The patient had a pre-fracture neuromuscular or musculoskeletal deficiency which limited the ability to perform objective functional measurements.<br>9. The patient was physically or mentally compromised (e.g., currently being treated for a psychiatric disorder, senile dementia, Alzheimer's disease, etc.) to the extent that the investigator judged the patient to be unable or unlikely to remain compliant.<br>10. The patient had an allergy to yeast-derived products.<br>11. The patient had received an investigational therapy or approved therapy |

| Table 2 – Inclusion Exclusion Criteria | |
|---|---|
| **Inclusion Criteria** | **Exclusion Criteria** |
| | for investigational use within 30 days of surgery or during the follow-up phase of this study.<br>12. The patient was a prisoner, known or suspected to be transient, or had a history of drug/alcohol abuse within the 12 months prior to screening for study entry.<br>13. The patient was pregnant or a female intending to become pregnant during the study period. A urine pregnancy test was to be administered within 21 days of the surgical visit to any female unless she was post-menopausal, had been sterilized, or was practicing a medically-accepted method of contraception.<br>14. The patient was deemed morbidly obese (body mass index [BMI] > 45 kg/m2). |

**Evaluations**

Clinical assessments include the primary effectiveness variable of fusion at the involved level, in addition to secondary pain/disability status, general health status, and graft site pain. Evaluations occurred preoperatively and at 2, 6, 9, 12, 16, 24, 36, and 52 week intervals as per the IDE protocol. Adverse events were evaluated over the course of the clinical trial. The protocol also included measurements of antibodies for anti-rh-PDGF-BB screening in the investigational group at baseline (prior to grafting procedure), visit 3 (day 7-21), visit 4 (week 6), visit 6 (week 12), and visit 8 (week 24). Success was determined from data collected during the initial 24 weeks of follow-up.

A summary of all study evaluations is provided in Table 3.

**Table 3 . Schedule of Study Assessments**

| Procedure | Screening Visit 1 Within 21 Days of Surgery | Surgery Visit 2 Day 0 | Post-Treatment Follow-up Evaluation Visit 3 Day 7-21 | Visit 4 Wk 6 ±7 Days | Visit 5 Wk 9 ±7 Days | Visit 6 Wk 12 ±7 Days | Visit 7 Wk 16 ±7 Days | Visit 8 Wk 24 ±14 Days | Visit 9 Wk 36 ±14 Days | Visit 10 Wk 52 ±14 Days |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X1 | | | | | | | | | |
| Urine Pregnancy Test (if applicable) | X | | | | | | | | | |
| Medical History / Non-Union Risk Factors | X | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Physical Examination of Foot / Ankle Region | X | X | X | X | X | X | X | X | X | X |
| Eligibility Criteria Verification | X | X | | | | | | | | |
| Identification of Target Bone Defect | X | | | | | | | | | |
| Serum for rhPDGF-BB Ab Testing | X2 | | X | X | | X | | X | | |
| Patient Randomization | | X3 | | | | | | | | |
| Intraoperative Report | | X | | | | | | | | |
| Volume of Graft Material Placed (if applicable) | | X | | | | | | | | |
| Physical Therapy | | | | X | X | X | X | X | X | |
| Radiographic Outcomes | X4 | X | X | X | X | X | X | X | X | X |
| CT Scans5 | | | | | X | | X | X | X | |
| Clinical / Functional Assessments6 | X | | | X | X | X | X | X | X | X |
| Pain Assessments | X | X | X | X | X | X | X | X | X | X |
| Quality-of-Life Assessments | X | | | X | | X | X | X | X | X |
| Adverse Events /Complications | | X | X | X | X | X | X | X | X | X7 |
| Concomitant Medications Review | X | X | X | X | X | X | X | X | X | X |

Ab = antibody; CT = computed tomography

1 Must have occurred prior to any study-specific procedures.

2 Peripheral blood sample for antibody evaluation was to be taken at baseline (prior to grafting), Day 7-21, Week 6, Week 12, and Week 24. For patients who tested positive for antibodies to rh-PDGF-BB, additional serum samples were to be requested in order to monitor patients until antibody titers returned to baseline. Patients testing positive for anti-rh-PDGF-BB antibodies were to be tested for neutralizing activity.

3 Interactive web randomization within 48 hours of scheduled surgery.

4 Pre-operative radiographic films may have been taken within 6 months of surgery. Radiologic assessments including osseous bridging across subchondral surfaces (primary endpoint for union), callus formation, % osseous bridging, and heterotopic bone formation were to be used to assess overall fusion site healing. Plain film radiographs were to be the primary source of data for clinical assessment of fusion.

5 CT scans (0.5-0.7 mm thickness at 0.2-0.3mm intervals, pitch of 0.7, and kVp of 130-140) were to be taken at Week 9, 16, 24, and 36. A baseline CT scan may have been taken to confirm that there were no radiographic signs of cysts that would exclude the patient. CT scans were to be assessed for radiographic union by independent radiologist.

6 VAS pain assessment, SF-12 quality-of-life assessment and functional assessments include range of motion, and weightbearing (Foot Function Index and AOFAS Hindfoot / Ankle scale).
7 Non-unions (therapeutic failures) after 12-month follow-up were to be collected

### Adverse Events

An adverse event was defined as "…clinical sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product." Exceptions were "… those events that are considered to be normal sequela to the surgical procedure". These surgical related events were not recorded as adverse events unless treatment was required or the event was considered to be "clinically significant" and included the following "clinical indicators": abnormal swelling or warmth by palpation at the fusion site; tenderness to palpation at the fusion site; motion at the fusion site; and pain with weight bearing at the fusion site. In addition, non-unions and delayed unions are reported as "Therapeutic Failures", and not documented as adverse events.

The Medical Dictionary for Regulatory Activities (MedDRA) was used to classify systemic adverse events while device-specific complications were displayed separately. The sponsor divided adverse events collected from this population into 7 subgroups:

1. Pre-treatment signs and symptoms
2. "Treatment Emergent Adverse Events" (TEAEs) defined as AEs reported on, or after, the day of surgery
3. "Complications" defined as complications associated with surgical procedures, a subset of the TEAEs
4. "Serious Complications"
5. Infections
6. Related TEAEs
7. Serious TEAEs

The incidence, severity, timing, and relationship of all TEAEs and device-specific complications are presented by treatment group within each subgroup. Analyses of adverse events were not considered as part of the primary endpoint, but are provided as a separate assessment of safety alone. According to the sponsor, "Graft harvest site pain scores are the primary safety endpoint; with operating room time and surgical wound infection rate as secondary safety endpoints."

Serious Adverse Events were monitored by the independent Medical Monitor (Averion) during the course of the study. Adverse Events reported for ongoing study data and the clinical investigational protocol was submitted on August 20 and September 20, 2008 to a Data Safety Monitoring Board (DSMB) for independent review. During these meetings, the Board raised concerns regarding the lack of a baseline CT; the fact that many subjects at the 6 month time-point were missing CT scans; and concerns that only certain adverse events were being documented as stated by the members of the DSMB. (FDA will further describe the DSMB's and FDA's potential concerns with adverse event reporting in a separate section below.)

For secondary surgical interventions, the protocol specified that these would be termed as "Therapeutic failures". Therapeutic failures were defined as to whether or not a revision secondary procedure or another therapeutic intervention (such as a bone stimulator) was required due to delayed or non-union. Patients with secondary procedures (use of bone stimulators or revision surgeries for delayed or non-union) were counted as CT fusion "failures"**.** A reoperation, elective removal, supplemental fixation or non-elective implant removal or other surgical procedures for any other indications other than delayed or non-union were not classified as “Therapeutic failures."  The FDA has expressed concerns to the sponsor regarding the inability of the defined “Therapeutic Failures” to capture other important safety events not related to delayed union or non-union and the need for a complete and objective categorization of secondary surgeries.

**Statistical Analysis Plan**

Randomization and Blinding
The randomization was in a 2:1 ratio of investigational to control patients. The randomization was stratified by clinical center, surgical site (hindfoot vs. ankle), and non-union risk factors (none vs. any of: obesity, diabetes, previous hindfoot/ankle surgery, or smoking history).

As per the protocol, neither investigators nor patients were blinded after the surgery, primarily because of the second surgical site necessary for collection of the iliac crest grafts. The lack of patient and surgeon blinding in this study is an important limitation of the study design and an unaddressed source of bias.  The lack of blinding could potentially have led to reporting bias among patients and investigators, in favor of the investigational device or against the control. This may be particularly problematic for subjective assessments such as patient reported outcomes. For radiographic measures, the radiologists were blinded as to the treatment received.

Hypotheses Tested
The null hypothesis states that Augment is inferior to autologous bone graft and was tested using a two-sample binomial test.  This was a non-inferiority trial with a 1-sided test at the 0.05 significance level using a 10% margin required by FDA.  The primary objective was to demonstrate non-inferiority in the primary endpoint (CT fusion) at 24 weeks after surgery. Secondary endpoints were assessed using a closed-testing procedure.  If all endpoints were non-inferior, superiority was then tested.

The original statistical analysis plan states that the primary analysis would be performed using the Intent to Treat (ITT) dataset defined as all randomized subjects who receive study treatment post-randomization, with the Per Protocol (PP) dataset being confirmatory. [N.B. However, this PMA utilizes the modified Intent to Treat (mITT) dataset (defined  as all randomized patients who were eligible, properly randomized, and received treatment according to the study protocol) as the primary effectiveness analysis dataset, with the revised ITT dataset (all randomized patients) being presented as supportive evidence.

According to the data presented, the sponsor achieved their primary endpoint – non-inferiority in fusion by CT at 24 weeks using this mITT (but missed their primary endpoint for non-inferiority by the ITT as described below).  Superiority at this, or other time points, for non-inferiority was not established.

Analysis Populations
Three different analysis datasets (ITT, safety, and PP) were defined in the original statistical plan approved in the IDE with the primary analysis to be performed using the ITT dataset and PP being confirmatory.

- Intent to Treat (ITT).  All randomized subjects who receive treatment post-randomization. Patients who are randomized but determined to be unable to be treated will be classified

as surgical screening failures and excluded. Subjects analyzed according to treatment randomized.
- Safety. All subjects who received study treatment.
- Per protocol (PP). All eligible subjects with at least one effectiveness observation and followed through week 24. This dataset will exclude visits with documented protocol deviations.

However, in the PMA, the names and definitions of these analysis datasets are different:
- Modified Intent to Treat (mITT). All randomized subjects who were eligible, properly randomized, and received treatment according to the protocol. Excludes intra-operative screen failures. Subjects are analyzed according to treatment received.
- Safety. Subset of ITT dataset with all patients treated with either Augment or autologous bone graft. Subjects analyzed according to treatment received.
- Intent to Treat (ITT). All randomized subjects, including intra-operative screen failures and patients randomized but never treated. Subjects analyzed according to treatment randomized.

[It should be noted that the modified ITT dataset described in the clinical study report is somewhat of a misnomer; it would be more appropriately described as a Per Protocol analysis population, due to analysis by treatment received, not randomized, as well as for excluding subjects not treated according to protocol.]

The PMA is based on the final analysis of the data evaluated in the mITT population described above up to 24-week visits. The ITT population is presented by the sponsor as supportive evidence. There are additional data available after 24 weeks through 52 weeks postoperative. Patients who were "Therapeutic Failures" (patients with non- or delayed union requiring either revision surgery or bone stimulator) were considered failures for the primary endpoint. [N.B. FDA will ask the panel a question related to the usage of the mITT for the primary endpoint.]

<u>Statistical Success Criteria</u>
The primary endpoint of fusion (at least 50% osseous bridging as assessed via CT scan) was assessed at 24 weeks, with monitoring up to 12 months for safety. Non-inferiority of the proportion of therapeutic successes between treatment groups was assessed with a 1-sided hypothesis test at the 0.05 significance level using a 10% non-inferiority margin. If non-inferiority was shown, superiority was to be tested at the 1-sided 0.025 level. A closed-testing procedure was used to assess secondary endpoints in order to control the type I error. If all endpoints were statistically non-inferior, superiority was then tested.

<u>Sample Size Calculation</u>
The sample size was determined assuming a 1-sided test with a 0.05 significance level, 2:1 randomization, 10% non-inferiority margin, and an expected 24 week fusion rate of 85% for both treatment groups. The resulting sample size of 357 (238 Augment, 119 bone graft) gives 80% power. This was inflated to 396 to account for an anticipated 10% dropout. The statistical analysis plan allowed for the DSMB to conduct safety and effectiveness analyses of the data. The trial was allowed to terminate early for futility, but not for effectiveness, and therefore no formal stopping guidelines or adjustment to the overall type I error were specified. The conditional power was to be used for this determination. The DSMB also had the option to recommend an adjustment to the planned sample size if the interim data suggested that the initial sample size estimate was insufficient (due to a mis-specification of the underlying fusion rates).

Protocol Violations

There were a total of 1,457 violations for 456 subjects. The majority of these violations (69%) were either missed or out of window study visit (39% and 30% of total violations, respectively).

**Table 4 – Protocol Violations**

| **Type of protocol violation** | **Number** | **Percentage** |
|---|---|---|
| Not Done / Missed Visit | 570 | 39.12% |
| Done Out of Time Window | 443 | 30.40% |
| Subject Refused | 52 | 3.57% |
| MD Decision | 181 | 12.42% |
| Subsequent Unrelated Surgery | 0 | 0.00% |
| Adjuvant therapy | 2 | 0.14% |
| Steroids Interfering Medical Conditions | 12 | 0.82% |
| Medication Impact on Healing on Pain Assessment | 44 | 3.02% |
| Value Out of Range | 4 | 0.27% |
| Other | 149 | 10.23% |
| **Total** | **1,457** | **100.00%** |

Heterogeneity of Response by Center

The sponsor conducted a Breslow-Day test of homogeneity for odds ratios to examine the appropriateness of pooling; the *p*-values for the test for each of the three 24 week outcomes assessed are: CT fusion ($p$=0.091), radiographic fusion ($p$=0.558), and full complement clinical union ($p$=0.577). Centers with fewer than 10 subjects were pooled together as one pseudo-center. A subsequent assessment of potential heterogeneity of response by center was explored via a logistic regression analysis for each outcome using treatment, site, and a treatment-by-site interaction. The results from the CT fusion outcome failed to converge due to a quasi-separation points (resulting from some sites with 0% or 100% fusion). The sponsor proposed two methods to overcome this: pooling the affected sites into the pooled sites group, and pooling the affected sites into a single affected sites group. Both the Breslow-Day and logistic regression assessments were conducted on both pooling approaches, and the results do not identify a statistically significant interaction by site. The sponsor concluded that the results from different clinical centers could be pooled.

Major Statistical Concerns

The main statistical concern with the trial revolves around the robustness of the primary effectiveness endpoint; this is manifested in two aspects. First, while the primary endpoint is statistically significant for non-inferiority in the mITT analysis dataset, it is not statistically significant in the ITT analysis dataset. Second, the results of the primary analysis are highly sensitive to the impact of missing data, despite the relatively low rate of missing data.

Long-term Follow-up of Primary Endpoint

While the primary endpoint (evidence of fusion) was statistically significant for non-inferiority in the mITT analysis population at 24 weeks, statistical significance was not obtained at 36 weeks.

This difference appears to be driven by the increased number of Autograft subjects demonstrating fusion between 24 and 36 weeks relative to the smaller increase for Augment subjects over the same time period. The sponsor states that this is explained by the higher proportion of Augment subjects missing 36 week data (and therefore imputed as therapeutic failures; 24 month CSR, p 277). The data supports this interpretation, as there are 17 Augment subjects with missing data at 36 weeks compared to only 3 Autograft subjects. However, when the 36 week data is analyzed restricted to subjects with complete data, the Augment cohort has a success rate of 67.9% (165/243) compared to an Autograft cohort success rate of 70.9% (95/134); this difference of -3.0% remains statistically non-significant ($p$=0.078). The protocol did not conduct CT scans at 52 weeks, preventing comparison at this further time-point.

**Table 5 – Statistical analysis of primary outcome**

| **Time-point** | **Augment (N=260)** | **Autograft (N=137)** | **Non-inferiority *p*-value** |
|---|---|---|---|
| 24 weeks | 61.2% | 62.0% | 0.038 |
| 36 weeks | 63.5% | 69.3% | 0.202 |

(based on mITT analysis population)

<u>Lack of Statistical Significance in the ITT Analysis Population</u>

As discussed above, there are differences between the analysis populations described in the protocol and those presented in the analysis. When asked for clarification on this issue, the sponsor stated that the protocol initially proposed an ITT definition, but that FDA had conveyed that the sponsor's proposed definition was more in line with a mITT population and that the sponsor could present it in the PMA. The sponsor further states that the only subjects excluded were either never treated, intra-operative screening failures, or should have been removed by the treating physician. They further explain that these decisions were made in a blinded fashion (i.e. the sponsor was unaware of treatment assignment and outcome measures when making these decisions).

FDA believes that the ITT analysis population as defined in the PMA should be considered the primary analysis. In addition, FDA advised the sponsor at the IDE stage that both analysis populations should be supportive of non-inferiority. Note that the ITT analysis population preserves the benefits of randomization, while the mITT analysis population does not (due to excluding subjects for mis-randomization or not receiving treatment according to protocol.)

| Table 6- Percentage of subjects with fusion (by 24 week CT scan) | | | | | |
|---|---|---|---|---|---|
| **Analysis population** | **Augment** | **Autologous bone graft** | **Difference (Augment – autologous bone graft)** | **1-sided 95% lower bound** | **Non-inferiority *p*-value** |
| **mITT (N=397)** | 61.2% (159/260) | 62.0% (85/137) | -0.8% | -9.3% | 0.038 |
| **ITT (N=434)*** | 57.9% (165/285) | 60.4% (90/149) | -2.5% | -10.7% | 0.065 |

The sponsor addressed the issue of the ITT population narrowly missing statistical significance. They point out that the variance of the test statistic is tied in with the underlying rate. They stated that they standardized the non-inferiority margin between the expected 85% and the observed 62% in terms of the standard error; their conclusion is that a 10% margin at 85% is approximately the same as a 14.8% margin at 65%, and that the lower bound in the ITT population meets this standardized criterion. [Please note that FDA does not consider this retrospective adjustment to the non-inferiority margin to be appropriate, and considers the margin of 10% pre-specified in the protocol to be the relevant comparison value.]

<u>Sensitivity of Results to Missing Data</u>

The number and percentage of subjects with missing primary outcome data is presented in the table below. The trial had a relatively low rate of missing data (5%-7%) which was relatively balanced between the two treatment arms.

| Table 7- Missing data (primary outcome) by treatment group and analysis population | | |
|---|---|---|
| **Analysis population** | **Augment** | **Autograft** |
| **mITT (N=397)** | (6.2%) 16/260 | (7.3%) 10/137 |
| **ITT (N=434)** | (4.6%) 13/285 | (4.7%) 7/149 |

The primary analysis imputed any missing observations for the primary outcome as Therapeutic Failures. In addition, a sensitivity analysis was conducted to explore the sensitivity of the primary analysis to alternative assumptions regarding missing data. The results of the sensitivity analyses for the impact of missing data on the primary endpoint in the mITT analysis were presented twice by the sponsor: once with the initial submission and again in a submission with extended follow-up. The tables summarizing this sensitivity analysis are presented below.

| Table 8 – Sensitivity analysis of primary outcome (based upon mITT) | | | | | |
|---|---|---|---|---|---|
| **Model** | **Augment (n=260)** | **Autograft (N=137)** | **Difference (Augment – Autograft)** | **1-sided 95% lower bound** | **Non-inferiority *p*-value** |
| Primary Endpoint | 61.2% | 62.0% | -0.9% | -9.3% | 0.038 |
| 1: LOCF | 62.7% (163/260) | 65.0% (89/137) | -2.3% | -10.6% | 0.063 |
| 2: Impute missing to success | 66.9% (174/260) | 69.3% (95/137) | -2.4% | -10.5% | 0.061 |
| 3: Assuming best case for Augment* | 66.9% (174/260) | 62.0% (85/137) | 4.9% | -3.5% | 0.002 |
| 4: Assuming worst case for Augment ** | 61.2% (159/260) | 69.3% (95/137) | -8.2% | -16.4% | 0.358 |
| 5. Observed | 64.9% (159/245) | 66.9% (85/127) | -2.0% | -10.5% | 0.062 |

* Imputes missing Augment as successes and missing Autograft as failures
** Imputes missing Augment as failures and missing Autograft as successes

FDA analysis based upon ITT analysis population:

| Table 9 – Sensitivity analysis of primary outcome (from follow-up submission) | | | | | |
|---|---|---|---|---|---|
| **Model** | **Augment (n=285)** | **Autograft (N=149)** | **Difference (Augment – Autograft)** | **1-sided 95% lower bound** | **Non-inferiority *p*-value** |
| 1:Primary Endpoint | 57.9% (165/285) | 60.4% (90/149) | -2.5% | -10.7% | 0.065 |
| 2: Impute missing to success | 62.5% (178/285) | 65.1% (97/149) | -2.6% | -10.6% | 0.065 |
| 3: Assuming best case for Augment* | 62.5% (178/285) | 60.4% (90/149) | 2.1% | -6.1% | 0.007 |
| 4: Assuming worst case for Augment ** | 57.9% (165/285) | 65.1% (97/149) | -7.2% | -15.2% | 0.284 |

* Imputes missing Augment as successes and missing Autograft as failures
** Imputes missing Augment as failures and missing Autograft as successes

The primary analysis assessed missing primary endpoint data as therapeutic failures (denoted by the blue dot in the lower left hand corner of the plot below). In addition, the sponsor conducted a sensitivity analysis of the primary endpoint: all missing imputed as Therapeutic Successes (upper-right hand corner), Augment best case (all Augment missing as successes and all ABG as failures – lower right hand corner), Augment worst case (all Augment missing as failures and all ABG as successes – upper left hand corner), last observation carried forward (purple asterisk), and observed data/complete case. This sensitivity analysis was conducted using the mITT analysis population.

To supplement this sensitivity analysis, FDA conducted a tipping point analysis looking at all possible combinations of missing data imputation. On the graph below, the horizontal axis represents the number of missing Augment subjects considered successes (from zero to the total missing of 15); the 10 missing ABG subjects are shown similarly on the vertical axis. Points denoted with a red circle represent imputation combinations which are not supportive of non-inferiority at the 0.05 significance level; points denoted with a solid blue circle are those which are supportive of non-inferiority. Also shown are the primary analysis (all as failures; green square), last observation carried forward (LOCF; purple asterisk), and missing completely at random (MCAR – conducted by using the complete case results and assuming all missing subjects would have had the same likelihood of success as observed subjects; green triangle). This graph suggests that the trial may not be particularly robust to missing data; for the most part, only imputation combinations which assume that the missing Augment subjects have a higher success rate than missing ABG subjects are supportive of non-inferiority. The conclusion is similar when using the ITT analysis population (results not shown).

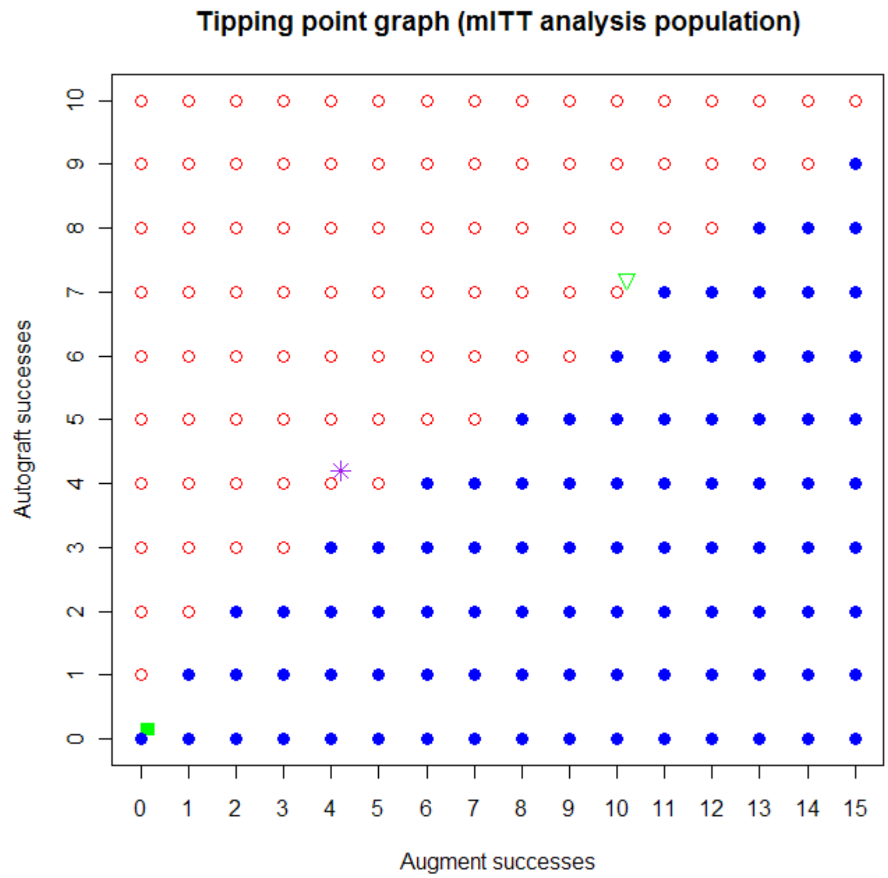



**Figure 1 – Tipping point sensitivity analysis to assess potential impact of missing data**

Sample Size Mis-estimation

To some degree, both the lack of significance in the ITT analysis population and the sensitivity to missing data are the result of the sponsor's mis-estimation of the sample size of the trial. Initially, the sample size was estimated assuming that the fusion rate in each treatment group would be approximately 85%; however, the observed rates were approximately 62%. As the primary endpoint is the difference in fusion rates (which are binomial proportions), the variance of the test statistic is tied to the value of the success rate. As a result, the fact that the observed rates were different from the expected values resulted in the variance of the test statistic being increased. Essentially, the trial was under-powered for the primary endpoint because the sample size was determined assuming a much smaller variance than was actually observed.

The sponsor addresses this difference between the expected and observed values, although they do not specifically discuss its potential impact on the sensitivity to missing data. They point out that, had the trial been powered for rates of 62%, the required sample size would have been increased to over 700 total subjects. However, the sponsor does not appear to address why the observed and expected rates are so divergent.

The protocol specifies that the independent data monitoring committee (DMC) had the option to recommend an increase in the sample size in the event that the success rate was mis-estimated (based upon interim blinded data). However, at some point after initiating the trial, the sponsor elected to remove this option. As a result, the sponsor does not appear to have been aware of this mis-estimation and the resulting implications for the power of the trial until after the trial had been completed. The minutes from the DMC meeting suggest that part of the rationale for removing this option is that the company was concerned that any interim look at the data may have led to FDA questioning the validity of the blind, or imposing statistical penalties on the trial.

**Statistical Summary**

Overall, there are several potential concerns regarding the robustness of the trial's primary endpoint (evidence of fusion by CT scan). Specifically, while the results were statistically significant for non-inferiority at 24 months, statistical significance was not retained at 36 months. Further, statistical significance was attained only in the mITT analysis population, not in the ITT analysis population. Finally, the results of the "tipping point" sensitivity analysis suggest that the results are extremely sensitive to the potential impact of missing data. Taken together, these issues raise concerns regarding the robustness of the trial's primary effectiveness endpoint, complicating an assessment of the effectiveness of the Augment device.

The primary concern regarding the sensitivity of the trial to alternative assumptions of missing data is that the primary analysis imputing all missing observations as Therapeutic Failures. While this approach is conservative in a traditional superiority analysis, it has the opposite effect in a non-inferiority trial because it makes the two treatment groups more similar. As a result, demonstrating that a trial is robust to alternative imputation methods is even more important in a non-inferiority trial than in a superiority trial, as the optimum imputation strategy for non-inferiority trials remains an open area in the clinical trial / statistical literature. The sponsor did provide multiple imputation models, however we believe that they do not fully address the underlying issue of missing data in non inferiority trials.

The primary concern regarding the analysis population similarly addresses an open area of research in the clinical trial / statistical literature. The ITT analysis population is traditionally viewed as optimal for superiority trials, but the issue of the optimal analysis for non-inferiority trials (ITT, mITT, As Treated, PP) remains undecided, because it is not always clear which analysis population will be conservative or non-conservative in a non-inferiority trial. Thus, demonstrating similarity of results and statistical inference is even more important in a non-inferiority trial than in a superiority trial. [FDA will be asking for input on the studies, statistical designs including the robustness of the results the statistical significance in the ITT dataset and mITT datasets, and the sensitivity of the results to differing assumptions regarding missing data.]

**CLINICAL STUDY RESULTS**
(Includes elaboration on several of the results/methods discussed in the statistical section above)

**Patient Accounting**

The prospective, randomized controlled clinical trial included a total of 456 patients screened and 435 randomized (331 were from the US and 104 were from Canada.) There are three patient populations that the sponsor separately accounts for (mITT, ITT, and Safety) and analyzes according to a modified grouping different from the original plan (PP, ITT, and Safety). These are described in the Analysis Population discussion on page 15. Because one patient was excluded post-treatment after randomization, the ITT population consists of 434 patients. Of these, 285 were implanted with the investigational device and 149 received the control treatment. The Safety dataset consists of 414 randomized and treated patients (272 investigational and 142 controls), after 20 of the randomized subjects were either intra-surgical screen exclusions or not treated. The mITT population, submitted by the sponsor for the PMA as the primary endpoint analysis, consists of 397 patients (414 patients in the Safety group minus an additional 17 subjects excluded post-operatively) divided into 260 investigational and 137 controls. The mITT group was used to determine the success or failure of the primary endpoint, without supportive validation from the other datasets.

A total of 38 sites participated in the study, but one site withdrew prior to the study closure. Of the 25 investigational patients, and 12 control patients who were excluded from the study, 17 investigational and 9 controls were excluded after randomization and have undergone surgical implantation. Because these patients did not meet the sponsor's definition of "Therapeutic Failure" based on non-union or delayed union, they were excluded from the study. For example, there were investigational subjects with infection at the fusion site, or who required a second surgery. There were 10 patients (7 investigational and 3 controls) randomized but excluded prior to receiving treatment.

Two subjects did not receive the randomized treatment: one subject randomized to Augment received Autograft, and one subject randomized to Autograft received Augment.

**Table 10 - Analyses Population**

| | **Total** | **Augment** | **Autograft** |
|---|---|---|---|
| **ITT** | 434 | 285 | 149 |
| – Not treated | 20 | 13 | 7 |
| **Safety** | 414 | 272 | 142 |
| – Excluded from analysis | 17 | 12 | 5 |
| **mITT** | 397 | 260 | 137 |

The sponsor has provided reasons for patient exclusion as categorized in the table below:

| Table 11 – Reasons for Patient Exclusion | | | |
|---|---|---|---|
| **Exclusion cause** | | **Augment** | **Bone graft** |
| Intra-operative and immediate post-surgical failure | Too much or prohibited hardware | 9 | 5 |
| | Midfoot procedure | 3 | 2 |
| | Hind foot plus ankle fusion | 2 | 1 |
| | Too much graft material used | 0 | 1 |
| | Use of allograft | 1 | 0 |
| | Infection at fusion site | 1 | 0 |
| | Second procedure required | 1 | 0 |
| | Early immobilization | 1 | 0 |
| Excluded prior to treatment | Patient withdrew consent | 4 | 1 |
| | Not medically cleared | 1 | 2 |
| | Investigative site closure | 1 | 0 |
| | Use of a prohibited medication | 1 | 0 |
| | | | |
| | **Totals** | **25** | **12** |

Twenty-four subjects (19 Augment, 5 autograft) discontinued participation. The reasons for discontinuation are provided in the following table:

| Table 12 – Reasons for Subject Discontinuation | | | |
|---|---|---|---|
| **Discontinuation Category** | **Total** | **Augment** | **Autograft** |
| Subject or Investigator request | 8 | 5 | 3 |
| Inability to return for follow-up | 1 | 0 | 1 |
| Non-compliance with protocol | 2 | 2 | 0 |
| Lost to follow-up | 5 | 5 | 0 |
| Death | 1 | 1 | 0 |
| Revision surgery required | 7 | 6 | 1 |
| TOTAL | 24 | 19 | 5 |

After an FDA deficiency request, the sponsor provided the following table which presents the patient accounting data for the 435 randomized, treated patients at 24 and 52 week follow-up:

| Table 13 – Patient Accounting (ITT) | | | | |
|---|---|---|---|---|
| | **24 weeks** | | **52 weeks** | |
| | **Investigational** | **Control** | **Investigational** | **Control** |
| Number of Patients Enrolled | 285 | 149 | 285 | 149 |
| Theoretical Follow-up | 243 | 133 | 243 | 133 |
| Cumulative Deaths | 0 | 0 | 0 | 0 |
| Failures (Cumulative)[1] | 0 (25) | 0 (12) | 0 (25) | 0 (12) |
| Expected | 243 | 133 | 243 | 133 |
| Actual[A] | 242 | 132 | 243 | 133 |
| Percent Follow-up (%)[A] | 100 | 99 | 100 | 100 |
| Actual[B] | 1 | 1 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Percent Follow-up (%)[B] | 0 | 1 | 0 | 0 |

[A] = patients with complete data for each endpoint, evaluated per protocol, in the window time frame
[B] = patient visit(s) missed

The table above shows that the sponsor only considers "failures" for the device as those patients who where excluded prior and intraoperatively from the study, all of which occurred at Day 0, or time of surgery. There were no "Therapeutic Failures" defined by the sponsor as delayed or non-union. Because patients were only considered in the primary analysis and patient accounting if they had complete data for each endpoint and evaluated per protocol (Actual[A]), the study has 100% follow-up for both groups at 52 weeks. The number in the Actual[A] population (374) is different from the number of patients used for the mITT (397) and the ITT (434). Actual[B] should provide information on all patients with any follow-up data, an "all evaluated" accounting. The sponsor's method of accounting deviates significantly from what the FDA customarily requests for clinical data presentations. Moreover, FDA, per Guidance[4], usually requests a sensitivity analysis to assist in explaining, both clinically and statistically, the pooling of patients with incomplete outcome data with those who have complete data collected per protocol.

There were 17 patients (12 investigational and 5 controls) who where excluded from the study analyses post-operatively after receiving surgical implantation. These patients were withdrawn from the study prior to database lock in a blinded manner in order to "determine evaluability for statistical analysis" of a mITT effectiveness population. The time period that had elapsed from time of surgery to time of withdrawal was one year in all cases except one (3 months). Fifteen of these 17 patients had problems that occurred at time of surgery (surgery not performed according to protocol), but remained in the study with evaluations up until the point of withdrawal as part of the "safety" population. *If the number of such protocol violators and withdrawals is high, the FDA will question the overall quality of the trial and its execution.* FDA has advised the sponsor that it has not provided an accurate "all evaluated" patient accounting, and that the number of withdrawals, especially those patients who are one year post-treatment withdrawn for problems that occurred intraoperatively, significantly impacts the ability to determine true study success, and thereby device safety and efficacy.

**Demographics and Preoperative Characteristics**

The following table provides a summary and comparisons of demographic variables and patient preoperative characteristics between the Augment™ and Control groups. The sponsor did not enroll patients under pre-defined criteria for study measures. This includes the absence of a baseline CT scan for comparison.

**Table 14 – Demographics (ITT)**

| **Variable** | **All Patients (N=434)** | **Investigational (N=285)** | **Control (N=149)** |
|---|---|---|---|
| Gender | | | |
| Male | 216 (49.8%) | 132 (46.3%) | 84 (56.4%) |
| Female | 213 (49.1%) | 149 (52.3%) | 64 (43.0%) |
| Missing | 5 (1.2%) | 4 (1.4%) | 1 (0.7%) |
| Age (years) | | | |

4 http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072283.pdf

| | | | |
|---|---|---|---|
| N | 429 | 281 | 148 |
| Mean | 56.6 | 56.2 | 57.5 |
| Standard deviation | 14.09 | 14.56 | 13.15 |
| Median | 58.7 | 58.6 | 59.7 |
| | | | |
| BMI (kg / m^2) | | | |
| N | 434 | 285 | 149 |
| Mean | 30.8 | 30.7 | 31.1 |
| Standard deviation | 5.69 | 5.63 | 5.82 |
| Median | 30.0 | 30.0 | 31.0 |
| | | | |
| Affected Foot/Ankle | | | |
| Right | 222 (51.2%) | 142(49.8%) | 80 (53.7%) |
| Left | 189 (43.5%) | 130 (45.6%) | 59 (39.6%) |
| Bilateral | 18 (4.1%) | 9 (3.2%) | 9 (6.0%) |
| Missing | 5 (1.2%) | 4 (1.4%) | 1 (0.7%) |
| | | | |
| Foot/Ankle to be treated | 230 (53.0%) | 147 (51.6%) | 83 (55.7%) |
| Right | 199 (45.9%) | 134 (47.0%) | 65 (43.6%) |
| Left | 5 (1.2%) | 4 (1.4%) | 1 (0.7%) |
| Missing | | | |
| | | | |
| Age of Injury/Deformity at Baseline (Week) | | | |
| N | 270 | 177 | 93 |
| Mean | 279.6 | 261.1 | 314.8 |
| Standard deviation | 458.78 | 460.62 | 455.66 |
| Median | 115.2 | 96.4 | 132.9 |
| | | | |
| Description of Injury/Deformity | | | |
| Primary Arthritis | 149 (34.3%) | 93 (32.6%) | 56 (37.6%) |
| Rheumatoid Arthritis | 29 (6.7%) | 24 (8.4%) | 5 (3.4%) |
| Post-traumatic Injury/Deformity | 209 (48.2 %) | 139 (48.8%) | 70 (47.0%) |
| Ankylosing spondylitis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other | 42 (9.7%) | 25 (8.8%) | 17 (11.4%) |
| Missing | 5 (1.2%) | 4 (1.4%) | 1 (0.7%) |
| | | | |
| Risk Factors | | | |
| Smoking history within last five years | 105 (24.2%) | 71 (24.9%) | 34 (22.8%) |
| Obesity (BMI > = 30 kng/m2) | 210 (48.4%) | 132 (46.3%) | 78 (52.3%) |
| Previous revision surgery | 101 (23.3%) | 65 (22.8%) | 36 (24.2%) |
| Diabetes history (type 1 or 2) | 52 (12.0%) | 32 (11.2%) | 20 (13.4%) |

There were some differences noted between the two treatment groups with regards to gender, age, and age of injury/deformity requiring surgery. The male to female ratio was 132/149 in the Augment group, and 84/64 in the control group with a higher percentage of female subjects in the Augment group (52% vs. 43%). The mean age of injury/deformity at baseline for subjects in the control group (315 weeks) was higher than the mean age of subjects in the investigational group (261 weeks). Rates of obesity were similar, but showed a slight increase in the autologous bone graft group relative to the investigational group (52% vs. 46%). The sponsor performed sensitivity analyses for a comparison of outcomes using several of these demographic variables as subgroups. The sponsor compared the success rates for quartiles of injury age and concluded that, because there were large numbers of missing injury ages, there is no pattern to support treatment differences between the two groups. Because of underlying statistical concerns, FDA raised concerns to the sponsor about interpreting the significance of various subgroup analyses in supplement 25 of the IDE. Overall, differences noted between treatment groups do not appear to have an effect on the primary effectiveness analysis.

**Surgical and Discharge Information**

The type of anesthesia, procedure time, type of fusion, and amount of graft material used was similar between the treatment groups as shown in the table below. Control subject bone grafts were taken from the proximal tibia (50.4%), distal tibia (16.1%), calcaneus (13.9%), the iliac crest (11.7%), and “Other” (7.9%). “Other” sites include fibula (5), medial malleolus (2), talus (2), and “local bone” (2).

**Table 15 – Surgical and Discharge Information (mITT)**

| | **All Patients (N=434)** | **Augment (N=285)** | **Autograft (N=149)** |
|---|---|---|---|
| Type of anesthesia [1] | | | |
| General | 323 (81.4%) | 212 (81.5%) | 111 (81.0%) |
| Regional nerve block with sedation | 132 (33.2%) | 88 (33.8%) | 44 (32.1%) |
| Spinal | 51 (12.8%) | 34 (13.1%) | 17 (12.4%) |
| IV sedation | 21 (5.3%) | 15 (5.8%) | 6 (4.4%) |
| Other | 55 (13.9%) | 40 (15.4%) | 15 (10.9%) |
| | | | |
| Procedure time (hours) | | | |
| N | 397 | 260 | 137 |
| Mean | 1.8 | 1.8 | 1.9 |
| Standard deviation | 0.6 | 0.58 | 0.62 |
| Median | 1.8 | 1.8 | 1.8 |
| Min - Max | 0.6 - 5.1 | 0.6 - 5.1 | 0.8 - 3.8 |
| | | | |
| Autograft harvest site | | | |
| Iliac crest | 16 (4.0%) | 0 (0%) | 16 (11.7%) |
| Distal tibia | 22 (5.5%) | 0 (0%) | 22 (16.1%) |
| Proximal tibia | 69 (17.4%) | 0 (0%) | 69 (50.4%) |
| Calcaneus | 19 (4.8%) | 0 (0%) | 19 (13.9%) |
| Other | 11 (2.8%) | 0 (0%) | 11 (8.0%) |
| Not applicable | 260 (65.5%) | 260 (100.0%) | 0 (0%) |
| | | | |
| Type of fusion | | | |
| Ankle joint fusion | 152 (38.3%) | 100 (38.5%) | 52 (38.0%) |
| Subtalar fusion | 104 (26.2%) | 66 (25.4%) | 38 (27.7%) |

| | | | |
|---|---|---|---|
| Calcaneocuboid fusion | 3 (0.8%) | 3 (1.2%) | 0 (0%) |
| Talonavicular fusion | 23 (5.8%) | 14 (5.4%) | 9 (6.6%) |
| Double fusions (e.g. talonavicular and calcaneocuboid joints) | 30 (7.6%) | 20 (7.7%) | 10 (7.3%) |
| Triple arthrodesis(subtalar, talonavicular, and calcaneocuboid joints) fusion | 85 (21.4%) | 57 (21.9%) | 28 (20.4%) |
| Ankle-hindfoot fusion | 0 (0%) | 0 (0%) | 0 (0%) |
| | | | |
| Amount of graft material used | | | |
| 1 - 3 cc | 115 (29.0%) | 75 (28.8%) | 40 (29.2%) |
| 4 - 6 cc | 201 (50.6%) | 135 (51.9%) | 66 (48.2%) |
| 7 - 9 cc | 81 (20.4%) | 50 (19.2%) | 31 (22.6%) |

Note: Percents are based on the number of patients in the mITT population.
[1] Patients may have received more than one type of anesthesia.

The 397 patients can be partitioned on the basis of the joints that were to be fused during surgery. This distribution is shown in table 16.

**Table 16 – Breakdown of Joints Fused by Treatment Group**

| Joint(s) fused | Count | Percent of total | Augment count | Percent of Augment total | Autograft count | Percent of autograft total |
|---|---|---|---|---|---|---|
| Ankle | 152 | 38% | 100 | 38% | 52 | 38% |
| Subtalar | 104 | 26% | 66 | 25% | 38 | 28% |
| Calcaneocuboid | 3 | 1% | 3 | 1% | 0 | 0% |
| Talonovicular | 23 | 6% | 14 | 5% | 9 | 7% |
| Subtalar and calcaneocuboid | 2 | 1% | 1 | 0% | 1 | 1% |
| Subtalar and talonovicular | 23 | 6% | 16 | 6% | 7 | 5% |
| Calcaneocuboid and talonovicular | 5 | 1% | 3 | 1% | 2 | 1% |
| Subtalar, calcaneocuboid, and talonovicular | 85 | 21% | 57 | 22% | 28 | 20% |
| Total | 397 | 100% | 260 | 100% | 137 | 100% |

The distributions of the different combinations of fusions into the two treatment groups are similar. The following table (Table 17) shows the distribution of patients, based on total number of screws used, and which joints were fused, displayed by raw patient counts.

| Table 17 - Counts of Patients by Joint Fused and Number of Screws Used | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Joint(s) fused | Number of screws used | | | | | | | | Number of screws used | | | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Total | Treatment |
| Ankle | | 2 | 44 | 106 | | | | | | | 31 | 69 | | | | | 100 | Augment |
| | | | | | | | | | | 2 | 13 | 37 | | | | | 52 | Autograft |
| Subtalar | | 12 | 87 | 5 | | | | | | 7 | 56 | 3 | | | | | 66 | Augment |
| | | | | | | | | | | 5 | 31 | 2 | | | | | 38 | Autograft |
| C'cuboid | 1 | 1 | | 1 | | | | | 1 | 1 | | 1 | | | | | 3 | Augment |
| | | | | | | | | | | | | | | | | | 0 | Autograft |
| Tal-vic | | 3 | 18 | 2 | | | | | | 2 | 11 | 1 | | | | | 14 | Augment |
| | | | | | | | | | | 1 | 7 | 1 | | | | | 9 | Autograft |
| Subt/cc | | | 2 | | | | | | | | 1 | | | | | | 1 | Augment |
| | | | | | | | | | | | 1 | | | | | | 1 | Autograft |
| Subt/talvic | | | 3 | 6 | 9 | 4 | 1 | | | | 2 | 5 | 5 | 4 | | | 16 | Augment |
| | | | | | | | | | | | 1 | 1 | 4 | | 1 | | 7 | Autograft |
| Cc/talvic | | | 1 | 1 | 2 | 1 | | | | | 1 | | 2 | | | | 3 | Augment |
| | | | | | | | | | | | | 1 | | 1 | | | 2 | Autograft |
| Subt/cc/talvic | | 1 | 15 | 31 | 24 | 5 | 7 | 2 | | | 11 | 19 | 16 | 4 | 5 | 2 | 57 | Augment |
| | | | | | | | | | | 1 | 4 | 12 | 8 | 1 | 2 | | 28 | Autograft |
| Total | 1 | 19 | 170 | 152 | 35 | 10 | 8 | 2 | 1 | 10 | 113 | 98 | 23 | 8 | 5 | 2 | 260 | Augment |
| | | | | | | | | | 0 | 9 | 57 | 54 | 12 | 2 | 3 | 0 | 137 | Autograft |

The distribution of number of screws used is similar for the two treatment groups both overall (as shown in the bottom row of the table) and for each type of fusion performed.

**Distribution of estimated amount of graft material used.**

The following table shows the distribution of patients based on total estimated amount of graft material used and which joints were fused.

| Table 18 - Counts of patients by joint fused and estimated amount of graft material used | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Joint(s) fused | Estimated amount of graft material used | | | Estimated amount of graft material used | | | | |
| | 1-3 cc | 4-6 cc | 7-9 cc | 1-3 cc | 4-6 cc | 7-9 cc | Total | Treatment |
| Ankle | 31 | 105 | 16 | 21 | 71 | 8 | 100 | Augment |
| | | | | 10 | 34 | 8 | 52 | Autograft |
| Subtalar | 46 | 40 | 18 | 32 | 26 | 8 | 66 | Augment |
| | | | | 14 | 14 | 10 | 38 | Autograft |
| C'cuboid | 2 | 1 | | 2 | 1 | | 3 | Augment |
| | | | | | | | 0 | Autograft |
| Tal-vic | 18 | 5 | | 12 | 2 | | 14 | Augment |
| | | | | 6 | 3 | | 9 | Autograft |
| Subt/cc | 1 | 1 | | | 1 | | 1 | Augment |
| | | | | 1 | | | 1 | Autograft |
| Subt/talvic | 5 | 16 | 2 | 4 | 11 | 1 | 16 | Augment |
| | | | | 1 | 5 | 1 | 7 | Autograft |
| Cc/talvic | 3 | 1 | 1 | 1 | 1 | 1 | 3 | Augment |
| | | | | 2 | | | 2 | Autograft |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subt/cc/talvic | 9 | 32 | 44 | 3<br>6 | 22<br>10 | 32<br>12 | 57<br>28 | Augment<br>Autograft |
| Total | 115 | 201 | 81 | 75<br>40 | 135<br>66 | 50<br>31 | 260<br>137 | Augment<br>Autograft |

The distribution of estimated amount of graft material used is similar for the two treatment groups overall (as shown in the bottom row of the table). The distribution shows slightly smaller amounts of graft material for Augment and slightly larger amounts of graft material for autograft for all the fusion types with the exception of the triple fusions, which is reversed.

**SAFETY EVALUATION**

The safety of the investigational device for this PMA was assessed as a separate analysis population and was not part of the primary study endpoint. Safety was assessed by evaluating graft harvest site pain scores as the primary safety endpoint, and operating room time and surgical wound infection rate as secondary safety endpoints. Safety was also evaluated based on the nature and frequency of adverse events which occurred in the Augment™ group, as compared to those that occurred in the Control group. [N.B. Antibody test results were not considered as part of the safety evaluation endpoint; but will be presented separately below in a separate section. FDA will be asking several questions to the panel dealing with adverse events and safety issues.]

**All Adverse Events**

The adverse events, as shown in the tables below, are reported from the "Safety Population" which included 272 Augment™ patients and 142 Control patients enrolled in the multi-center clinical study. Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group. A total of 212 (77.9%) of Augment™ patients had at least one adverse event within 52 weeks versus 105 (73.9%) Control patients; although this does not reach statistical significance it may have clinical significance. A total of 657 events were reported in the Augment™ patients and 316 events were reported in the Controls. The 24-week data analysis was used as the primary effectiveness endpoint. The summary of AEs by SOC and PT in either treatment group is provided in Table 19.

**Table 19– Adverse Events Summary by MedDRA SOC and PT**

| System Organ Class Preferred Term | All Patients (N=414) | | Augment Bone Graft (N=272) | | Autologous Bone Graft (N=142) | |
|---|---|---|---|---|---|---|
| | Subjects | Events | Subjects | Events | Subjects | Events |
| Any Adverse Event | 317 (76.6%) | 973 | 212 (77.9%) | 657 | 105 (73.9%) | 316 |
| Blood and lymphatic system disorders | 2 (0.5%) | 2 | 1 (0.4%) | 1 | 1 (0.7%) | 1 |
| Cardiac disorders | 9 (2.2%) | 10 | 3 (1.1%) | 3 | 6 (4.2%) | 7 |
| Congenital, familial and genetic disorders | 2 (0.5%) | 2 | 1 (0.4%) | 1 | 1 (0.7%) | 1 |
| Ear and labyrinth disorders | 3 (0.7%) | 3 | 1 (0.4%) | 1 | 2 (1.4%) | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Endocrine disorders | 2 (0.5%) | 3 | 2 (0.7%) | 3 | 0 (0.0%) | 0 |
| Eye disorders | 5 (1.2%) | 6 | 2 (0.7%) | 3 | 3 (2.1%) | 3 |
| Gastrointestinal disorders | 52 (12.6%) | 66 | 35 (12.9%) | 45 | 17 (12.0%) | 21 |
| General disorders and administration site conditions | 56 (13.5%) | 61 | 37 (13.6%) | 40 | 19 (13.4%) | 21 |
| Hepatobiliary disorders | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Immune system disorders | 12 (2.9%) | 13 | 10 (3.7%) | 11 | 2 (1.4%) | 2 |
| Infections and infestations | 89 (21.5%) | 121 | 61 (22.4%) | 86 | 28 (19.7%) | 35 |
| Injury, poisoning and procedural complications | 104 (25.1%) | 125 | 67 (24.6%) | 82 | 37 (26.1%) | 43 |
| Medical device pain | 21 (5.1%) | 21 | 14 (5.1%) | 14 | 7 (4.9%) | 7 |
| Investigations | 9 (2.2%) | 9 | 6 (2.2%) | 6 | 3 (2.1%) | 3 |
| Metabolism and nutrition disorders | 8 (1.9%) | 9 | 4 (1.5%) | 5 | 4 (2.8%) | 4 |
| Musculoskeletal and connective tissue disorders | 166 (40.1%) | 276 | 117 (43.0%) | 193 | 49 (34.5%) | 83 |
| Arthralgia | 53 (12.8%) | 63 | 38 (14.0%) | 46 | 15 (10.6%) | 17 |
| Pain in extremity | 69 (16.7%) | 80 | 48 (17.6%) | 56 | 21 (14.8%) | 24 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 7 (1.7%) | 7 | 5 (1.8%) | 5 | 2 (1.4%) | 2 |
| Nervous system disorders | 58 (14.0%) | 65 | 43 (15.8%) | 49 | 15 (10.6%) | 16 |
| Psychiatric disorders | 16 (3.9%) | 18 | 11 (4.0%) | 13 | 5 (3.5%) | 5 |
| Renal and urinary disorders | 28 (6.8%) | 29 | 17 (6.3%) | 17 | 11 (7.7%) | 12 |
| Reproductive system and breast disorders | 3 (0.7%) | 3 | 1 (0.4%) | 1 | 2 (1.4%) | 2 |
| Respiratory, thoracic and mediastinal disorders | 25 (6.0%) | 30 | 14 (5.1%) | 15 | 11 (7.7%) | 15 |
| Skin and subcutaneous tissue disorders | 61 (14.7%) | 69 | 41 (15.1%) | 47 | 20 (14.1%) | 22 |
| Surgical and medical procedures | 14 (3.4%) | 16 | 9 (3.3%) | 9 | 5 (3.5%) | 7 |
| Vascular disorders | 27 (6.5%) | 29 | 18 (6.6%) | 20 | 9 (6.3%) | 9 |

There are 5 categories of adverse events in which the Augment group is greater than or equal to two percentage points higher than the Control group: immune system disorders (3.7% vs 1.4%); musculoskeletal and connective tissue disorders (43.0% vs 34.5%); arthralgia (14.0% vs 10.6%); pain in extremity (17.6% vs 14.8%); and nervous system disorders (15.8% vs 10.6%). Specifically, the Augment device group had a higher percentage of adverse events involving arthralgia and pain in the extremity (considered as “preferred terms” over the SOC). The correlation of high rates of pain measured as adverse events with secondary outcome measures for device effectiveness is unclear. Interestingly, infection and infestation rates between the 2 groups were fairly similar (Augment, 20.2% and Control, 18.3%). However, clinically this is a significant number of infections. No inferential statistical comparison of adverse events between investigational and control groups was performed.

There are 1.8% (5/272) of adverse events in Augment patients categorized as Neoplasms and 1.4% (2/142) in Control patients. [* N.B. Cancers will be discussed in a separate section due to their nature and the noted association between Regranex gel (also rhPDGF-BB) and the FDA-issued Early Communication, which indicated a possible link between multiple uses of Regranex and an increase in mortality from pre-existing cancers.]

**Serious Adverse Events**

Serious Adverse Events (SAEs) are defined as World Health Organization (WHO) Grade 3 or 4. There were a total of 57 SAEs reported within the "Safety" population. The proportion of patients having serious adverse events were similar for the investigational and control groups being 11.0% (30/272 subjects, 32 events) and 16.9% (24/142 subjects, 25 events), respectively. All but 5 (3 Augment and 2 Controls) were reported as recovered/resolved.

There were 3 Augment subjects and no Control subjects who were withdrawn from the study due to SAEs. The three Augment subjects were withdrawn for the following reasons: one infection noted during surgery, one death due to pulmonary embolism, and one bilateral Methicillin Resistant Staphylococcus Infection (MRSA) infection of both knees. Nine surgical wound infections were classified as SAEs: 4 Augment (in 3 patients) and 5 Controls. None of the SAEs by causality and outcome were attributed to be device related. However, one patient was categorized under Preferred Term as "Device Related Infection", but under the category Investigator Causality was listed as "Not Related". The table of treatment-emergent SAEs by MedDRA System Organ Class (SOC) and Preferred Term ( PT) is presented in Table 20 below.

**Table 20 – Summary of Treatment-Emergent Serious Adverse Events By MedDRA SOC and PT**

| System Organ Class Preferred Term | All Patients (N=414) | | Augment Bone Graft (N=272) | | Autologous Bone Graft (N=142) | |
|---|---|---|---|---|---|---|
| | Subjects | Events | Subjects | Events | Subjects | Events |
| Any Adverse Event | 49 (11.8%) | 74 | 28 (10.3%) | 45 | 21 (14.8%) | 29 |
| Cardiac disorders | 4 (1.0%) | 5 | 1(0.4%) | 1 | 3 (2.1%) | 4 |
| Acute myocardial infarction | 1(0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Atrial flutter | 1(0.2%) | 1 | 1(0.4%) | 1 | 0 (0.0%) | 0 |
| AV block complete | 1(0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Cardiac failure congestive | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Myocardial infarction | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Congenital, familial and genetic | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Congenital foot malformation | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Gastrointestinal disorders | 6 (1.4%) | 7 | 3 (1.1%) | 4 | 3 (2.1%) | 3 |
| Gastritis | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Gastrointestinal haemorrhage | 4 (1.0%) | 5 | 2 (0.7%) | 3 | 2 (1.4%) | 2 |
| Megacolon | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| General disorders and administration site conditions | 6 (1.4%) | 6 | 6 (2.2%) | 6 | 0 (0.0%) | 0 |
| Chest pain | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Impaired healing | 2 (0.5%) | 2 | 2 (0.7%) | 2 | 0 (0.0%) | 0 |
| Non-cardiac chest pain | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Pyrexia | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Cardiac chest pain | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Infections and infestations | 9 (2.2%) | 12 | 5 (1.8%) | 7 | 4 (2.8%) | 5 |
| Cellulitis | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Clostridium difficile colitis | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Infection | 1(0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Osteomyelitis | 3 (0.7%) | 3 | 1 (0.4%) | 1 | 2 (1.4%) | 2 |
| Pneumonia | 2 (0.5%) | 2 | 2 (0.7%) | 2 | 0 (0.0%) | 0 |
| Postoperative wound infection | 2 (0.5%) | 2 | 1 (0.4%) | 1 | 1 (0.7%) | 1 |
| | | | | | | |
| Staphylococcal infection | 2 (0.5%) | 2 | 1 (0.4%) | 1 | 1 (0.7%) | 1 |
| Injury, poisoning and procedural complications | 5 (1.2%) | 5 | 3 (1.1%) | 3 | 2 (1.4%) | 2 |
| Device related infection | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1(0.7%) | 1 |
| Medical device complication | 1 (0.2%) | 1 | 1(0.4%) | 1 | 0 (0.0%) | 0 |
| Overdose | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Postoperative wound infection | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Wound infection staphylococcal | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Investigations | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Prothrombin level abnormal | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Musculoskeletal and connective tissue | 9 (2.2%) | 9 | 7 (2.6%) | 7 | 2 (1.4%) | 2 |
| Foot fracture | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Joint instability | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Joint range of motion decreased | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Muscle strain | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Osteoarthritis | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Osteoporosis | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Pain in extremity | 3 (0.7%) | 3 | 3 (1.1%) | 3 | 0 (0.0%) | 0 |
| Neoplasms benign, malignant and unspecified (incl cyst) | 5 (1.2%) | 5 | 3 (1.1%) | 3 | 2 (1.4%) | 2 |
| Endometrial cancer | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Lung neoplasm malignant | 1 (0.2%) | 1 | 1(0.4%) | 1 | 0 (0.0%) | 0 |
| Prostate cancer | 2 (0.5%) | 2 | 2 (0.7%) | 2 | 0 (0.0%) | 0 |
| Renal cell carcinoma stage unspecified | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Nervous system disorders | 2 (0.5%) | 2 | 2 (0.7%) | 2 | 0 (0.0%) | 0 |
| Cerebrovascular accident | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Convulsion | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Psychiatric disorders | 2 (0.5%) | 2 | 1 (0.4%) | 1 | 1 (0.7%) | 1 |
| Alcohol withdrawal syndrome | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Suicide attempt | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Respiratory, thoracic and mediastinal | 4 (1.0%) | 5 | 1 (0.4%) | 1 | 3 (2.1%) | 4 |
| Atelectasis | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Chronic obstructive pulmonary disease | 1 (0.2%) | 2 | 0 (0.0%) | 0 | 1 (0.7%) | 2 |
| Hypoxia | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Pulmonary embolism | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Surgical and medical procedures | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Osteotomy | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Vascular disorders | 12 (2.9%) | 13 | 7 (2.6%) | 8 | 5 (3.5%) | 5 |
| Aortic stenosis | 1 (0.2%) | 1 | 0 (0.0%) | 0 | 1 (0.7%) | 1 |
| Deep vein thrombosis | 7 (1.7%) | 7 | 4 (1.5%) | 4 | 3 (2.1%) | 3 |
| Pulmonary embolism | 4 (1.0%) | 4 | 3 (1.1%) | 3 | 1 (0.7%) | 1 |
| Thrombosis | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |

There were 8 categories where rates differed in the Augment Group by greater than one percentage point: general disorders and administrative site conditions, which included chest pain, non-cardiac chest pain, cardiac chest pain, impaired healing and pyrexia (2.2% vs 0%); and musculoskeletal and connective tissue disorders, which includes foot fracture, joint instability, joint range of motion decreased, and muscle strain (2.6% vs 1.4%); and pain in extremity (1.1% vs 0%).

**Detailed Information on Specific Adverse Event Categories**

<u>Cancer Events</u>

In the randomized subject cohort, there were 7 events (5 investigational and 2 controls) noted as “Neoplasms” for this trial, with 5 of these categorized by the sponsor as Serious Adverse Events. Two patients with neoplasms in the investigational group were not considered as serious adverse events because the sponsor considered these of a “benign” nature (1 pre-cancerous hyperplastic colon polyp and 1 plantar fibroma).

This IDE study for Augment™ had exclusion criterion that only excluded patients for “untreated malignant neoplasm(s) at the surgical site, or was currently undergoing radio- or chemotherapy”. Therefore, it is possible that patients that received the device may have had pre-existing cancer at other sites, either distant from the surgical site and/or was not currently undergoing cancer treatment. A total of 5 cancer events occurred in 5 patients (1.8%) in the Augment™ group and a total of 2 cancer events occurred in 2 Control patients (1.4%) through 52 weeks. Although the rates in the investigational group appear to be higher than those in the control, they are not statistically different (but potentially may be clinically important due to the possibility of tumor promotion). Of these events, all were classified by the sponsor as not related to the device. There was no clear relationship to any demographic or other parameter among the Augment™ patients with cancers reported to 24 months according to gender (3 males and 4 females); time to diagnosis (range 20 days to 9 months); age at surgery (range 42-75). Brief summaries of the types of cancer cases and subsequent treatment, as well as a detailed table of the events (Table 21) are as follows:

**Table 21 - Summary of Cancer Events to 52 Weeks**

| Case ID | Patient No | Treatment Group | Sex | Age at Surgery | Surgery Fusion Type | Cancer Type | Time of Diagnosis Post-tx | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | Augment | M | 65 | Subtalar | Prostate | 7 months | Radiation | Recovered |
| | | Augment | F | 57 | Subtalar, Talonavicular and Calcaneocuboid | Breast | 4 months | Bilateral total mastectomy and 2 rounds chemotherapy | Unresolved Further information requested |
| | | Augment | M | 64 | Ankle | Prostate | 6 months | Chemotherapy | Unresolved Further information requested |
| | | Augment | F | 61 | Ankle | Hyperplastic Colon Polyp | 9 months | Removal | Resolved |
| | | Augment | F | 42 | Ankle | Plantar fibroma | 9 months | Removal | Resolved |
| | | Control | M | 75 | Ankle | Renal Cell Carcinoma | 20 days | Right ureterectomy and radical nephrectomy | Recovered |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| [redacted] | Control | F | 60 | Ankle | Endometrial cancer | 7 months | No additional information past diagnosis at time of biopsy | Unresolved Further information requested |

Investigational
The cancer types at 52 weeks listed by the sponsor as Serious Adverse Events (SAEs) include the following: two prostate cancers and one breast cancer. Further information on the two neoplasms listed under All Adverse Events (AAEs), but not classified as SAEs include one hyperplastic colon polyp and one plantar fibroma. Information on the 3 investigational patients with SAE cancer, revealed that there were 2 males and 1 female; 5.6 average months (4 to 7, range) time to diagnosis; 62 average age (57 to 65, range) at diagnosis; and subsequent treatments as outlined in the table above. Outcome on 2 of these 3 patients remain "unresolved". The most notable related parameter was the time to cancer diagnosis, all being within less than 9 months. Detailed information on the type of fusion procedure performed was provided.

Control
The cancer types seen in the control group were as follows: one renal cell carcinoma and one endometrial carcinoma. There was one male and one female; average 4 months (20 days and 7 months) to diagnosis; ages 60 and 75; and subsequent treatments as outlined in the table above.

Augment trial patients were excluded from study with the presence of "untreated malignant neoplasm(s) at the surgical site, or currently undergoing radio- or chemotherapy." The sponsor argues that this should not be a concern for the Augment device, given the lower concentrations used in the Augment trial as compared to the current study. FDA has asked the sponsor for additional information to justify this opinion. [N.B. The platelet-derived growth factor (rhPDGF-BB) protein family is a potent stimulator of cell proliferation. It plays a major role in cell-cell communication for normal development, blood vessel formation (angiogenesis) and also during pathological states such as uncontrolled angiogenesis as a characteristic of cancer. A MEDLINE review revealed reports of PDGF-BB specifically in association with breast, endometrial, renal cell, and prostate cancer[5]. [FDA will be asking questions related to the above information.]

Patient Deaths
There was 1 death in the investigational group and none in the control group through the 52 week reporting time. The patient (patient [redacted] case [redacted] died of a pulmonary embolism 14 days after surgery. This SAE was assessed as being "not related" to the study device. The following table (Table 22) provides all known information on the one death reported.

5 Ustach CV, et .al.: A potential oncogenic activity of PDGF D in prostate cancer progression. Cancer Research. March 1 (64):1722-1729, 2004.

| Table 22 - Summary of Deaths to 52 Weeks | | | | | | |
|---|---|---|---|---|---|---|
| **Case ID** | **Patient No** | **Treatment Group** | **Reported Term** | **Preferred Term** | **Investigator Causality** | **Event Outcome** |
| [redacted] | | Augment Bone Graft | PULMONARY EMBOLISM | Pulmonary Embolism | Not related | Death |

**Immunogenicity Summary**

A major potential safety concern with the administration of therapeutic proteins is the clinical consequences to patients who develop anti-drug antibodies. Although for most patients the presence of anti-drug antibodies appears to be benign, anti-drug antibodies have resulted in severe deficiency syndromes (pure red cell aplasia in erythropoietin treated patients), loss of efficacy and changes to pharmacokinetics/pharmacodynamics.
Platelet derived growth factors (PDGF-BBs) are involved in different functions, including embryonic development, hematopoiesis, blood vessel formation, and tumorigenesis. Knock-out of the PDGF-BB gene in mice is lethal to embryos due to massive hemorrhage and edema. Histological data from knock-out embryos revealed abnormal kidney glomeruli, capillary microaneurysms, cardiac muscle hypotrophy and placental defects for the lethality. PDGF-BB signaling is also important for cardiac development such as atrioventricular valves and capillaries in a murine model [6].

Antibody Monitoring
Antibodies to rhPDGF-BB was drawn at baseline, visit 3 (day 7-21), visit 4 (week 6), visit 6 (week 12), and visit 8 (week 24). Patient samples were analyzed with an ELISA designed to measure antibodies specific for rhPDGF-BB. However, the assay used to detect neutralizing antibody activity was a RIA, deficient in its capacity to evaluate the ability of antibodies to directly interfere with drug activity in vivo. The sponsor was unable to provide the sensitivity and specificity of the assays used. The following outline provides results for the two types of antibody studies evaluated. For patients testing positive for antibodies to rhPDGF-BB, additional serum samples were obtained until antibody titers returned to baseline.

1. **rhPDGF-BB Antibody Results:** Formation of antibodies to rhPDGF-BB was assessed in 423 patients. Anti-rhPDGF-BB binding antibodies were detected in 46 patients. The incidence of anti-rhPDGF-BB binding antibody formation was 13.1% (37 of 282 patients) for patients who received Augment bone graft compared to 3.5% (5 of 141 patients) for those who received autograft alone. Four of the Augment bone graft and two autograft recipients were antibody positive pre-treatment. Twelve of 282 patients (4.2%) who received rhPDGF-BB were still positive for binding antibodies at the end of the study (visit 8, month 6) whereas two of 141 (1.4%) of autograft patients were positive for binding antibodies at that time. Information on patient antibody status beyond six months is not available for most patients.

2. **Neutralizing Antibody Results:** A RIA neutralizing antibody assay was run on samples from patients with positive antibodies to rh-PDGF-BB. There were no positive neutralizing antibodies detected by this method. However the sponsor has been

[6] Van den Akker NM et al., PDGF-BB signaling is important for murine cardiac development: its role in developing atrioventricular values, coronaries, and cardiac innervation, 2008 Dev Dyn. Feb; 237 (2): 494-503

informed to develop a bioassay for the evaluation of anti-drug neutralizing antibodies, as the current method is unacceptable.

<u>Assessment of Immunogenicity Assays</u>
The sponsor validated an assay to screen for the presence of antibodies that bind PDGF-BB. They are developing a cell based bioassay to assess whether those antibodies interfere with the receptor ligand interaction (neutralizing antibody assay). Therefore the incidence of neutralizing antibodies is not known at this stage. At the 6 months follow up, 13 patients (11 Augment and 2 Controls) still had a titer of binding antibodies and were asked to submit at least 2 additional serum samples, 3 months apart. The sponsor states that of 14 subjects with elevated antibodies at six months, 13 have since returned to baseline. However, 7/14 (50%) patients who had positive antibodies at the end of the 6 month study were negative at preceding visits.

There was 15/47 (31.9%) Tier 3 subjects with + ADA antibodies that were at titers of 1:400 or 1:800. All of these returned to normal by the second follow-up past 24 weeks, except 1, who has not followed up to date. Of the 19 Augment patients who were both ADA + and considered as device failures, 8 of these had titers > 1:400 or 1:800 (42%). In the control group none of the subjects who were considered as device failures had high antibody titers. Adverse events associated with high titer ADA + Augment device failures consisted of 2 infections, 1 hardware complications and 5 that were not available through adverse events review.

Patients were followed for only a short time post-treatment and the sponsor did not follow patients till they reverted to baseline antibody status as is currently recommended by the Laboratory of Immunology (CDER/FDA). To date, the sponsor has not submitted information on the patients' neutralizing antibody status by a neutralizing bioassay. FDA will ask the panel about the immune response findings and the potential need for additional testing or information.

**All Device-Related Adverse Events**

There was only 1 patient ([redacted]reported who had an adverse event classified as a complication and further classified as a device-related complication over 52 weeks in the Augment group 1/272 (0.37%) (as compared to none in the Control group). This was categorized as a moderate severity "adverse reaction to Augment (nausea and diarrhea)" and coded as a "hypersensitivity". However one additional patient [redacted] was categorized under Preferred Term as "Device Related Infection", but under the category Investigator Causality was listed as "Not related". FDA has sought clarification from the sponsor on this event in September 03, 2010 deficiency letter.

The following table outlines this adverse event classified as device-related complications by category for each treatment group.

**Table 23-Summary of Device-Related AE to 52 Weeks**

| System Organ Class Preferred Term | All Patients (N=414) | | Augment Bone Graft (N=272) | | Autologous Bone Graft (N=142) | |
|---|---|---|---|---|---|---|
| | Subjects | Events | Subjects | Events | Subjects | Events |
| Any Adverse Event | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Immune system disorders | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Hypersensitivity | 1 (0.2%) | 1 | 1 (0.4%) | 1 | 0 (0.0%) | 0 |

Serious Device-Related Adverse Events

There were no patients who had serious adverse events classified as complications and further classified as serious device-related complications over 52 weeks. Therefore, both treatment groups reported a 0% incidence of serious device complications by the sponsor using their methods. FDA has discussed with the sponsor that some device complications potentially were misclassified as non-serious device-related adverse events.

"Complications" or Procedure-Associated Adverse Events

"Complications" were those AEs that were associated with the surgery, or Procedure-Associated AEs, a subset of the TEAE dataset. These were further determined by the Medical Monitor as being associated with the surgery, study device, or reduction, fixation or immobilization. The investigator considered device-related complications as immune reactions, device particulate irritations, or exuberant bone formation outside the fusion space. However, the investigator did not report routine post-surgical findings such as pain, warmth, tenderness, weight-bearing status, motion of fusion site, and healing status as AEs, unless considered as clinically significant. FDA has related its potential concerns to the sponsor about their reporting of events.

"Complications" were reported for 23.5% of Augment patients compared to 29.6% of Controls. "Complications" reported in more than 2% of patients (highlighted in table below) in either treatment group were as follows: hypoaesthesia (2.9% of Augment patients and 2.8% of Controls); postoperative wound infection (0.7% of Augment patients and 2.8% of Controls); wound dehiscence (2.6% of Augment patients and 1.4% of Controls); impaired healing (2.2% of Augment patients and 2.1% of Controls); cellulitis (1.5% of Augment patients and 2.1% of Controls); and deep vein thrombosis (DVT) (2.2% of Augment patients and 2.1% of Controls).

An overall summary of all complications associated with surgical procedures is presented in the table below.

**Table 24 - Complications Associated with the Surgical Procedure**

| System Organ Class<br>Preferred Term | All Patients (N=414) | | Augment Bone Graft (N=272) | | Autologous Bone Graft (N=142) | |
|---|---|---|---|---|---|---|
| | Subjects | Events | Subjects | Events | Subjects | Events |
| Any Adverse Event | 106 (25.6%) | 136 | (23.5%) | 81 | (29.6%) | 55 |
| General disorders and administration site conditions | 12 (2.9%) | 12 | (2.9%) | 8 | (2.8%) | 4 |
| Impaired healing | 9 (2.2%) | 9 | (2.2%) | 6 | (2.1%) | 3 |
| Inflammation | 1 (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Necrosis | 1 (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Tenderness | 1 (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Immune system disorders | 2 (0.5%) | 2 | (0.4%) | 1 | (0.7%) | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Drug hypersensitivity | 2 (0.5%) | 2 | (0.4%) | 1 | (0.7%) | 1 |
| Infections and infestations | 24 (5.8%) | 26 | (4.8%) | 14 | (7.7%) | 12 |
| Abscess | 1 (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Cellulitis | 7 (1.7%) | 7 | (1.5%) | 4 | (2.1%) | 3 |
| Infection | 2 (0.5%) | 2 | (0.7%) | 2 | (0.0%) | 0 |
| Osteomyelitis | 3 (0.7%) | 3 | (0.4%) | 1 | (1.4%) | 2 |
| Post procedural infection | 1 (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Postoperative wound infection | 6 (1.4%) | 6 | (0.7%) | 2 | (2.8%) | 4 |
| Stitch abscess | 1 (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Wound infection | 3 (0.7%) | 3 | (0.4%) | 1 | (1.4%) | 2 |
| Wound infection bacterial | 1 (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Wound infection staphylococcal | 1 (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Injury, poisoning and procedural complications | (8.7%) | 40 | (7.4%) | 22 | (11.3%) | 18 |
| Arteriovenous graft site haematoma | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Blister | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Blood blister | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Device related infection | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Graft complication | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Incision site infection | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Medical device complication | (0.5%) | 2 | (0.4%) | 1 | (0.7%) | 1 |
| Medical device pain | (0.5%) | 2 | (0.0%) | 0 | (1.4%) | 2 |
| Nerve compression | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Open wound | (0.5%) | 2 | (0.7%) | 2 | (0.0%) | 0 |
| Post procedural cellulitis | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Post procedural complication | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Post procedural discharge | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Post procedural haematoma | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Post procedural infection | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Post procedural oedema | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Postoperative wound complication | (0.5%) | 2 | (0.7%) | 2 | (0.0%) | 0 |
| Postoperative wound | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| infection | | | | | | |
| Procedural pain | (1.0%) | 4 | (0.7%) | 2 | (1.4%) | 2 |
| Stitch abscess | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Wound complication | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Wound decomposition | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Wound dehiscence | (2.2%) | 9 | (2.6%) | 7 | (1.4%) | 2 |
| Wound haemorrhage | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Wound infection | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Musculoskeletal and connective tissue | (1.4%) | 6 | (1.5%) | 4 | (1.4%) | 2 |
| Bone pain | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Joint range of motion decreased | (0.5%) | 2 | (0.7%) | 2 | (0.0%) | 0 |
| Limb deformity | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Muscular weakness | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Pain in extremity | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Nervous system disorders | (5.3%) | 22 | (5.1%) | 14 | (5.6%) | 8 |
| Hypoaesthesia | (2.9%) | 12 | ( 2.9%) | 8 | ( 2.8%) | 4 |
| Nerve injury | (0.2%) | 1 | ( 0.4%) | 1 | ( 0.0%) | 0 |
| Neuralgia | (0.5%) | 2 | ( 0.7%) | 2 | ( 0.0%) | 0 |
| Neuritis | (0.2%) | 1 | ( 0.0%) | 0 | ( 0.7%) | 1 |
| Neuropathy peripheral | (0.2%) | 1 | ( 0.0%) | 0 | ( 0.7%) | 1 |
| Paraesthesia | (0.2%) | 1 | ( 0.0%) | 0 | ( 0.7%) | 1 |
| Paralysis | (0.2%) | 1 | ( 0.4%) | 1 | ( 0.0%) | 0 |
| Peroneal nerve injury | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Sensory loss | (0.5%) | 2 | (0.7%) | 2 | (0.0%) | 0 |
| Respiratory, thoracic and mediastinal disorders | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Pulmonary embolism | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Skin and subcutaneous tissue disorders | (1.7%) | 8 | (1.8%) | 6 | (1.4%) | 2 |
| Blister | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Erythema | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Scar pain | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Skin disorder | (0.2%) | 1 | (0.0%) | 0 | (0.7%) | 1 |
| Skin irritation | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Skin necrosis | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |
| Skin ulcer | (0.2%) | 2 | (0.4%) | 2 | (0.0%) | 0 |
| Surgical and medical procedures | (1.4%) | 6 | (1.1%) | 3 | (2.1%) | 3 |
| Osteotomy | (0.7%) | 3 | (0.7%) | 2 | (0.7%) | 1 |
| Wound drainage | (0.7%) | 3 | (0.4%) | 1 | (1.4%) | 2 |
| Vascular disorders | (2.9%) | 13 | (2.9%) | 9 | (2.8%) | 4 |
| Deep vein thrombosis | (2.2%) | 9 | (2.2%) | 6 | (2.1%) | 3 |
| Pulmonary embolism | (0.7%) | 3 | (0.7%) | 2 | (0.7%) | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Thrombosis | (0.2%) | 1 | (0.4%) | 1 | (0.0%) | 0 |

Infections
For all adverse events, there are a high number of infections and infestations in both groups, but this is slightly higher in the investigational group by about 2 percentage points (22.4 vs. 19.7%). As these patients are being treated with surgical fusions, this is of potential clinical concern. However when the investigator divides this major SOC category into separate subgroup analyses, it is noted that the Control group has a higher rate of "Complications" associated with surgical procedure coded as infections (4.8% for Augment (13 patients) compared to 7.7% for Controls (11 patients)). It is not clear how Infections and Infestations are greater in the investigational group when all adverse events are considered and greater in the Control group when only "Complications" are considered. Moreover, there are 10 subcategories of Infections and Infestations listed as "Complications". It is not clear how distinctions are made between each category. For example, how are the distinctions between an infection, a post-procedural infection, and a post-operative infection respectively each made. Surgical wound infections were reported in 8.8% of Augment patients in the mITT population, compared with 9.5% of Controls. Nine surgical wound infections met the criteria for serious adverse events. Of these 9 serious surgical wound infections, 4 (3 patients; 1.1%) were in the Augment treatment group and five (5) were in the autologous bone graft treatment group. There was one serious wound infection at the bone graft harvest site.

Vascular Events
The incidence of serious "complications" coded as vascular disorders was reported as 13 events for 12 patients or by treatment group of 2.9% Augment and 2.8% for Controls (DVT: 2.2% Augment versus 2.1% Control; Pulmonary Embolus: 0.7% Augment versus 0.7% Control; and Thrombosis: 0.4% Augment and 0% Control). The categories of "DVT" and "Thrombosis" were higher for the investigational group. When these same terms (DVT and Pulmonary Embolus) are categorized as serious TEAEs the incidence of events is quite different (DVT: 1.5% Augment versus 2.1% Controls and Pulmonary Embolus: 1.1% Augment versus 0.7% Controls).

Secondary Surgical Interventions
Secondary surgical procedures were termed as "Therapeutic failures" by the sponsor. Therapeutic failures were determined as to whether or not a secondary procedure or other therapeutic intervention (such as a bone stimulator) was required due to delayed or non-union. A reoperation, elective removal, supplemental fixation or non-elective implant removal or other surgical procedures were not classified as "Therapeutic failures." The 24 week therapeutic failure rate was 9.2% of Augment patients, compared with 10.9% of Controls, supporting non-inferiority ($p$<0.001) according to the sponsor. Thirteen patients (8 Augment; 5 Controls) were noted as receiving either a bone stimulator or revision surgery. There were 5 secondary procedures relating to revision surgeries to correct insufficient fusion (4 Augment; 1 Control). There were 8 secondary procedures relating to revision surgeries to correct insufficient fusion (4 Augment; 1 Controls). This is shown in the table below.

**Table 25 -Listing 35 Secondary Procedures as a Result of Delayed or Non-Union**

| Treatment Group | Date of Study Procedure | Date of Invalid Procedure | Weeks from Study to | Type of Procedure | 24-Week CT Fusion*(A/T/S/C) |
|---|---|---|---|---|---|

| | | | Invalid Procedure | | |
|---|---|---|---|---|---|
| Autologous Bone Graft | 06AUG2007 | 08FEB2008 | 26 | Bone stimulator | N/_/_/_ |
| Autologous Bone Graft | 18JUN2008 | 24MAR2009 | 39 | Bone stimulator | N/_/_/_ |
| Augment Bone Graft | 08SEP2008 | 28MAY2009 | 37 | Bone stimulator | N/_/_/_ |
| Augment Bone Graft | 08OCT2008 | 09JUL2009 | 39 | Bone stimulator | _/N/N/_ |
| Augment Bone Graft | 14OCT2008 | 28APR2009 | 28 | Revision surgery | N/_/_/_ |
| Augment Bone Graft | 26DEC2007 | 12MAY2008 | 19 | Revision surgery | _/_/_/_ |
| Augment Bone Graft | 09OCT2008 | 09JUN2009 | 34 | Revision surgery | _/Y/Y/N |
| Autologous Bone Graft | 21AUG2007 | 18MAR2008 | 30 | Revision surgery | N/_/_/_ |
| Augment Bone Graft | 22JAN2008 | 22JUL2008 | 26 | Revision surgery | N/_/_/_ |
| Autologous Bone Graft | 05MAY2008 | 26OCT2008 | 24 | Bone stimulator | _/N/_/N |
| Augment Bone Graft | 25NOV2008 | 13APR2009 | 19 | Bone stimulator | _/N/_/N |
| Autologous Bone Graft | 31DEC2008 | 28MAY2009 | 21 | Bone stimulator | _/Y/Y/Y |
| Augment Bone Graft | 31DEC2008 | 11MAY2009 | 18 | Bone stimulator | N/_/_/_ |

Patients with secondary procedures (use of bone stimulators or revision surgery) were counted as CT fusion “failures” regardless of the actual observed value. At week 24, 24 (9.2%) of mITT Augment patients were declared therapeutic failures, compared with 15 (10.9%) of Controls. The non-inferiority hypothesis in the mITT and ITT populations was reported as $p<0.001$ in both populations.

There were other subjects whom the sponsor’s protocol should have included in the analysis as therapeutic failures: an Augment subject with infection at the fusion site; an Augment subject who required a second surgery for revision; and a Control subject who received too much graft material. Also, because of the way secondary surgeries were categorized as not device related, such events as these are excluded from the analysis of failures. The sponsor also did not consider reoperations as failures unless they were associated with non-union or delayed union, although several cases involved secondary surgeries at the treated level for other reasons. [FDA disagrees with the sponsor’s interpretation and/or reporting and will be asking question relating to adverse events during the panel meeting. FDA has communicated its concerns about such reporting in the past to the sponsor.]

**Safety Evaluation Summary**

A safety summary is provided in both narrative and table forms for the "safety population" (414 treated subjects) out to 52 weeks. The sponsor subdivides adverse events collected from this population into 7 subgroups. Analyses of adverse events were not considered as part of the primary endpoint, but are provided as a separate assessment of safety alone.

The following table presents a summary of the adverse events analyzed at 52 Weeks as subgroups defined by the sponsor.

**Table 26 – Summary of Adverse Events Analyzed By Subgroups**

| | Augment | | Autologous bone graft | | *p*-value |
|---|---|---|---|---|---|
| | Subjects | Events | Subjects | Events | |
| **Pre-treatment signs and symptoms** | 7 (2.6%) | 7 | 4 (2.8%) | 5 | >0.999 |
| **Treatment Emergent Adverse Events (TEAEs)** | 212 (77.9%) | 657 | 105 (73.9%) | 316 | 0.393 |
| **Complications** | 96 (35.3%) | 149 | 55 (38.7%) | 77 | 0.519 |
| **Serious complications** | 14 (5.1%) | 18 | 9 (6.3%) | 10 | 0.654 |
| **Infections** | 23 (8.5%) | 28 | 16 (11.3%) | 18 | 0.378 |
| **Related TEAEs** | 6 (2.2%) | 9 | 6 (4.2%) | 10 | NA |
| **Serious TEAEs** | 28 (10.3%) | 45 | 21 (14.8%) | 29 | 0.201 |

A total of 212 (77.9%) of investigational patients had at least one Treatment Emergent Adverse Event (TEAE) within 24 weeks versus 105 (73.9%) control patients (rates not statistically different). Through 24 weeks a total of 657 events were reported in the investigational patients and 316 events were reported in the controls. The proportion of patients having serious adverse events was similar for the investigational and control groups being 11.0% (30/272 subjects, 32 events) and 16.9% (24/142 subjects, 25 events) respectively.

Complications (classified as a TEAE subgroup) were reported as 23.9% and 30.3% or the investigational and control groups, respectively. There were 40 treatment-emergent infections (7.7%) (21/272) Augment subjects with 24 events, compared to 9.9% (14/142) autologous bone graft subjects with 16 events, with 9 surgical wound infections that were further classified as SAEs (4 Augment (in 3 patients) and 5 autologous bone graft). The investigational group had a lower rate in the category of graft site related pain adverse events.

In summary, the primary safety concerns are the cancer and immunological events in patients treated with Augment™ when compared to the control group. [However, there may be additional major potential safety issues that FDA has not been able to evaluate at this point. In addition, the number of patients with high titer antibody results and the uncertain results of the neutralizing assay also raise potential clinical concerns.]

## EFFECTIVENESS EVALUATION

### Primary Endpoint (Overall Clinical Success)

The primary effectiveness endpoint of the trial was CT fusion rate at 24 weeks of the "full complement" of joints in the modified intent to treat population (mITT). The fusion status of patients was assessed at 9, 16, 24, and 36 weeks following surgery. Fusion success was defined as greater than 50% osseous bridging at 24 weeks. Patients who received secondary procedures (bone stimulators or revision surgery) were considered as failures. No other criteria for failure were applied. CT scans were assessed by independent radiologists and tested for intra-rater consistency. However, the method used to read CT scans for osseous bridging, termed as "novel"[7] was not externally validated. There were also no baseline CT data for comparisons.

As was introduced above, in the statistical plan section, the sponsor used the following populations for analyses of the primary effectiveness endpoint in the PMA (that was a change from the approved IDE protocol and was implemented without our approving the change from the FDA in an approved modification to the IDE):

<u>Modified Intent to Treat (mITT)</u>
Patients excluded from the per-protocol analysis had major protocol deviations (i.e., did not meet the inclusion/exclusion criteria, received the wrong study treatment, or had other major protocol deviations that could potentially affect clinical outcomes). However, this group also excluded post-operative patients that had received the device, but had additional joint fusions.

<u>Intent to Treat (ITT)</u>
All randomized subjects, including intra-operative screen failures and patients randomized but never treated. Subjects analyzed according to treatment randomized.

The investigational group was found to be statistically non-inferior to the control group in the mITT group (p=0.038; the one-sided 95% lower bound of difference with autologous bone graft was -9.3%), but not in the ITT group (p=0.065; the one-sided 95% lower bound of difference with autologous bone graft was -10.7%). At week 24, 61.2% of Augment patients were deemed successful by CT scan in the full complement of joints, compared with 62.0% of patients treated with autologous bone graft.

The following table describes the success rates and the number in each treatment group for the overall effectiveness of the "Full-Complement" analysis. Study success is evaluated based on data from the 24-week follow-up evaluation.

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[7] Coughlin MJ, et al.: Comparison of radiographs and CT scans in the prospective evaluation of the fusion of hindfoot arthrodesis. Foot Ankle In. Oct 27(10):780-7, 2006.

| Table 27 – Summary of Full-Complement Analyses | | | | |
|---|---|---|---|---|
| | Percentage of subjects with fusion (by 24 week CT scan) | | | |
| **Treatment group** | **Augment** | **Autologous bone graft** | **1-sided 95% lower bound** | **p-value** |
| **mITT** | 61.2% (159/260) | 62.0% (85/137) | -9.3% | 0.038 |
| **ITT*** | 57.9% (165/285) | 60.4% (90/149) | -10.7% | 0.065 |

*The percentage of subjects with fusion is smaller in both treatment groups in the ITT analysis population relative to the percentages in the mITT population; this is primarily due to the inclusion of 37 additional subjects, many of whom are considered therapeutic failures).

At 24 weeks following surgery, for all patients for whom any data are available (mITT), the overall success for the Augment™ group is 61.2% as compared to 62.0% overall success rate for the Control group, at which time-point, non-inferiority was achieved.

However for the ITT group, at 24 weeks, the overall success rate dropped to 57.9% in the Augment™ group and 60.4% in the Control group. Within this group, non-inferiority was not achieved (with a one sided 95% lower bound CI of -10.7 and a p-value of 0.065).

Additional analyses were done by the sponsor to evaluate the primary endpoint, classifying the fusion status of each joint considered individually as an “all joints” analysis and a post hoc evaluation of osseous bridging at each time-point for the percentage bridging noted.

From the radiographic information provided on osseous bridging, the investigational device does not appear to be effective (or non-inferior) for the primary endpoint of “full complement” evaluation at 50 and 75% osseous bridging for any time-point, except the 24 week, in both ITT and mITT groups. At all time points for both groups, the CT Fusion Rate by Joint and Visit success for the Control group was greater than corresponding investigational group success rates for 14 out of 21(66%) analyses in the mITT group and 20 of 21 (95%) of the ITT group.

Moreover, for the assessment of Osseous Bridging by CT in both the mITT and the ITT populations when the most complete bridging (75 to 100%) is considered, the Control group again outperforms the investigational group at all time points, except for 2 of the 36 analyses (Talonavicular and the Calcaneocuboid fusion at 24 weeks).

With the “all joint” analysis, the sponsor states that, as an example, a non-evaluable subtalar joint is counted as a failure in the full complement analysis but would only count as one of three data points in the “all joint” analysis. Fusion was assessed by CT at 24 weeks for 50% osseous bridging. For the “all joints” assessment, 66.5% of joints treated with Augment were deemed successful, compared with 62.6% of joints treated with autologous bone graft.

| Table 28 – Summary of All-joints Analyses | | | | |
|---|---|---|---|---|
| | Percentage of subjects with fusion (by 24 week CT scan) | | | |
| **Treatment group** | **Augment** | **Autologous bone graft** | **1-sided 95% lower bound** | **p-value** |
| **mITT** | 66.5% (262/394) | 62.6% (127/203) | -2.9% | <0.001 |
| **ITT** | 66.2% (273/419) | 64.6% (137/212) | -6.1% | <0.001 |

When fusion is assessed with a time-to-event analysis, the curves (see Figure below, from sponsor) suggest a similar pattern but with a possible advantage to Autograft (not statistically significant by Wilcoxon-Gehan test for superiority; *p*=0.1047).

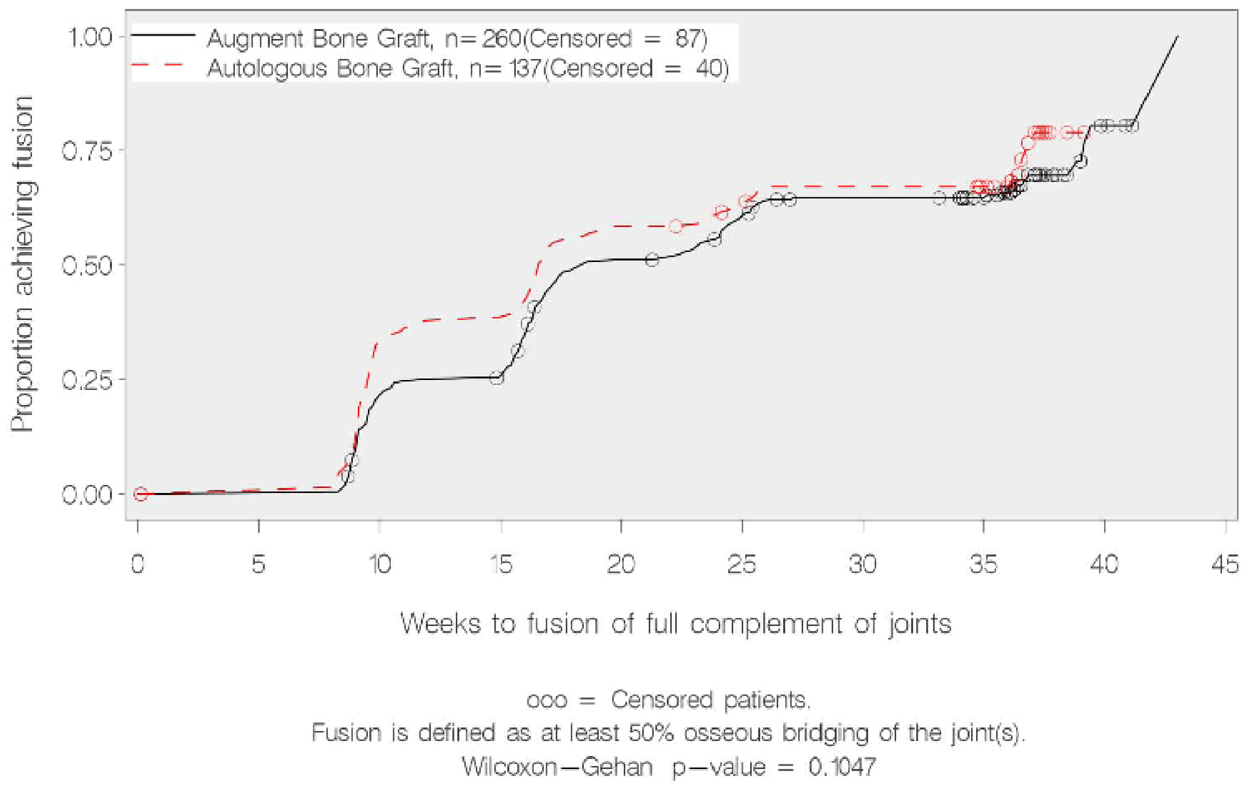


**Figure 2 – Weeks to Fusion of Full Complement of Joints**

**Secondary Effectiveness Endpoints**

<u>Fusion Success Rate at 24 weeks by Plain Radiographs</u>
In addition to the CT evaluations, the fusion success rate at 24 weeks was determined by plain radiographs. Success was defined as 3 of the 4 radiographic aspects (medial, lateral, anterior/superior, posterior/inferior) demonstrating osseous bridging with disappearance of the joint space at each treated joint. Each plane was classified as fused, not fused, or not evaluable. Below is a summation table of this data.

| Table 29– Summary of Fusion Success Rate by Plain Radiographs | | | | |
|---|---|---|---|---|
| | | Augment | Autologous bone graft | *p*-value |
| 3 aspects | mITT | 30.8% | 32.8% | 0.054 |
| | ITT | 28.4% | 31.5% | 0.070 |
| 2 aspects | mITT | 60.8% | 66.4% | 0.194 |
| | ITT | 57.9% | 63.8% | 0.200 |

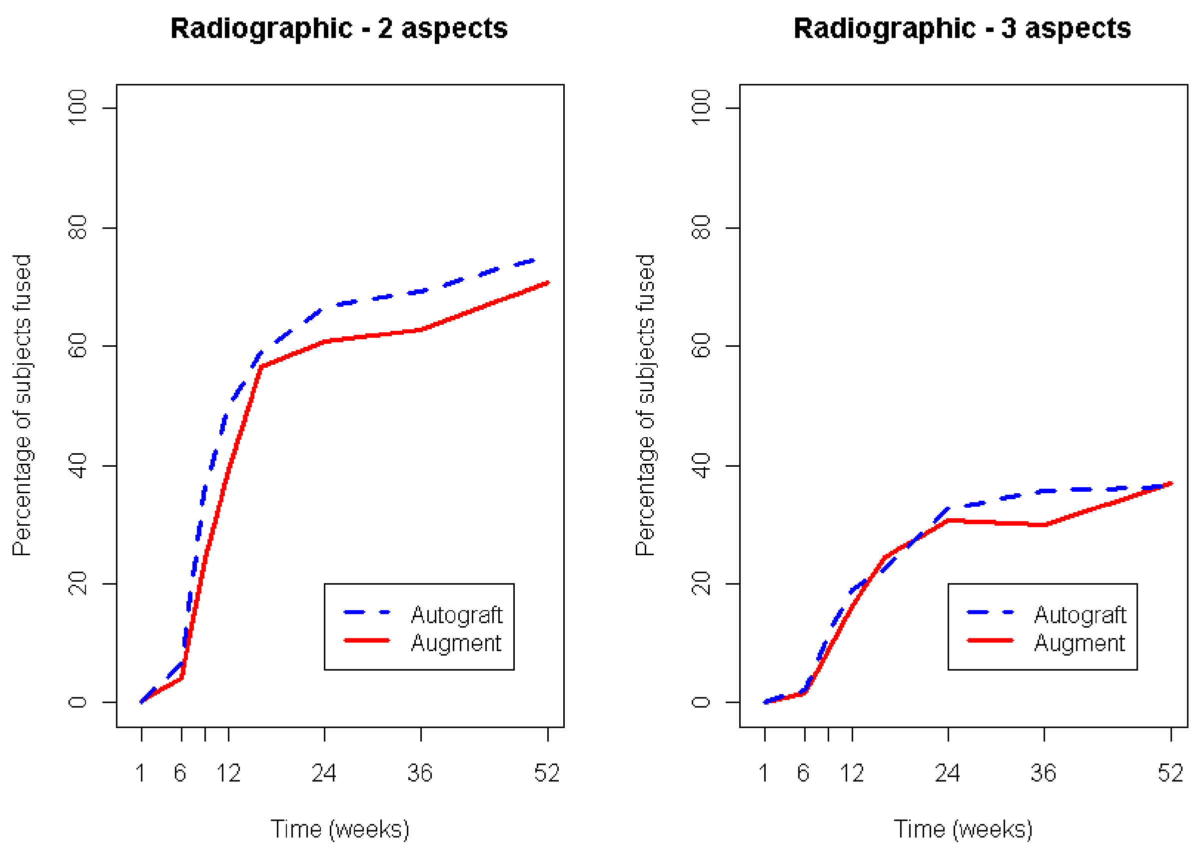


**Figure 3 – Radiographic 2 and 3 aspects percentage of subjects fused over time**

For success at 3 aspects, Control patients achieved 32.8% radiographic union at the full complement of joints, compared with 30.8% of Augment patients in the mITT population. Less stringent criteria for success defined fusion as osseous bridging with disappearance of the joint space at 2 radiologic aspects. For success at 2 aspects, Control patients achieved 66.4% radiographic union at the full complement of joints, compared with 60.8% of Augment patients in the mITT population. Therefore, in the mITT population, as well as the ITT population, Controls had numerically higher overall fusion success rates by plain radiographic evaluations than Augment. Tests for non-inferiority using these endpoints for the full complement of joints were just outside the boundary for statistical significance as noted with the p-values above.

Plain radiographs were also used to assess evidence of abnormal bone formation at the fusion site. Abnormal bone formations at week 24 were most commonly reported at the ankle joint (6.3% of Augment patients and 4.0% of Controls). The most common abnormal bone formations at the ankle joints were further specified as "periosteal reaction loosening versus infection positive", "soft tissue swelling and effusion"; and "abnormal tibial periosteal reaction suspicious for infection" in 1 Control patient and 5 Augment patients. This information was not used to assess the "Safety" dataset.

Clinical Success-Clinical Healing Status
To assess for "clinical union", clinical and functional assessments were performed using a check-box with five possible outcomes: "union", "evidence of progressive healing", "delayed union", "non-union", and "un-interpretable". "Clinical union" was achieved if the investigator selected "union" for the clinical healing status at a particular visit. Determination was based on physical examination and available data. Clinical assessments were performed on a patient level (clinical assessment) and on a per-joint treatment level (algorithms as used with CT scans and radiographs).

**Table 30– Summary of Clinical Union**

| **Secondary outcomes at 24 weeks (mITT group)** | **Augment** | **Autologous bone graft** | ***p*-value** |
|---|---|---|---|
| **Healing status of union** | 83.1% (216/260) | 83.9% (115/137) | 0.010 |
| **Clinical union (full complement)** | 82.3% (214/260) | 83.2% (114/137) | 0.011 |
| **Clinical union (all joints)** | 83.5% (329/394) | 83.3% (169/203) | <0.001 |

At week 24, 83.1% of Augment Bone Graft patients in the mITT population were assessed as having "clinical healing" at the patient level (Table 19 above), compared with 83.9% of Controls. Non-inferiority was statistically significant in both the mITT (p=0.010) and ITT (p=0.005) populations.

Composite Success
According to the sponsor, a patient was declared a composite success if:

- Surgical treatment was completed per protocol
- Patient was declared to have union or evidence of progressive healing at week 24
- CT scans for the full complement of joints demonstrated osseous bridging assessed as at least 25% at week 24
- The patient experienced no SAEs of possible relation to study treatment by week 24
- The patient's VAS pain assessment was less than 20 mm at the graft harvest site at week 6 and after
- There was no need for secondary therapeutic intervention at or before week 24

Please note that this VAS assessment was not performed for the ankle fusion site or for weight bearing for the treatment group or the control in this composite success measure, thereby raising concerns regarding its clinical utility.

At week 24, 66.9% of Augment patients had achieved composite success, compared with 66.4% of Controls in the mITT population as shown in the table below. The non-inferiority test for composite success was statistically significant in the mITT population (p=0.017) and in the ITT population (p=0.029).

**Table 31– Summary of Composite Success**

| Secondary outcomes at 24 weeks (mITT group) | Augment (Success Rate) | Autologous bone graft (Success Rate) | *p*-value |
|---|---|---|---|
| **Composite outcome (clinical, functional, radiologic)** | 66.9% (174/260) | 66.4% (91/137) | 0.017 |
| **Rate of clinical success*** | 74.6% (194/260) | 78.1% (107/137) | 0.071 |

The sponsor's composite endpoint (table 32) for clinical success was defined as improved pain (VAS scale) with weight bearing compared to baseline combined with no need for revision surgery. At week 24, the clinical success rate was 74.6% for Augment patients and 78.1% for Controls in the mITT population. The non-inferiority test for clinical success was not statistically significant in the mITT population (p=0.071). Control group success rates for clinical success at all periods were greater than corresponding investigational group success rates in the mITT population.

**Table 32- Clinical Success by Visit - mITT and ITT Populations**

| | | | mITT Population | | | |
|---|---|---|---|---|---|---|
| | **All Patients (N=397)** | **Augment Bone Graft (N=260)** | **Autologous Bone Graft (N=137)** | **Rate Difference*** | **Non-inferiority p-value (95% upper bound)** | **Superiority p-value (97.5% upper bound)** |
| Day 7-21 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.0 | NA (0.0%) | NA (0.0%) |
| Week 6 | 91 (22.9%) | 55 (21.2%) | 36 (26.3%) | -5.1 | 0.141 (-12.6%) | >0.999(-14.0%) |
| Week 9 | 253 (63.7%) | 164 (63.1%) | 89 (65.0%) | -1.9 | 0.054 (-10.2%) | >0.999(-11.8%) |
| Week 12 | 277 (69.8%) | 181 (69.6%) | 96 (70.1%) | -0.5 | 0.024 (-8.4%) | >0.999 (-9.9%) |
| Week 16 | 293 (73.8%) | 188 (72.3%) | 105 (76.6%) | -4.3 | 0.107 (-11.8%) | >0.999(-13.3%) |
| Week 24 | 301 (75.8%) | 194 (74.6%) | 107 (78.1%) | -3.5 | 0.071 (-10.8%) | >0.999(-12.2%) |

| | All Patients (N=397) | Augment Bone Graft (N=260) | ITT Population<br>Autologous Bone Graft (N=137) | Rate Difference* | Non-inferiority p-value (95% upper bound) | Superiority p-value (97.5% upper bound) |
|---|---|---|---|---|---|---|
| Day 7-21 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.0 | NA (0.0%) | NA (0.0%) |
| Week 6 | 96 (22.1%) | 56 (19.6%) | 40 (26.8%) | -7.2 | 0.259 (-14.3%) | >0.999(-15.7%) |
| Week 9 | 259 (59.7%) | 167 (58.6%) | 92 (61.7%) | -1 | 0.083 (-11.3%) | >0.999(-12.8%) |
| Week 12 | 285 (65.7%) | 186 (65.3%) | 99 (66.4%) | -1.2 | 0.033 (-9.1%) | >0.999(-10.6%) |
| Week 16 | 303 (69.8%) | 194 (68.1%) | 109 (73.2%) | -5.1 | 0.141 (-12.6%) | >0.999(-14.0%) |
| Week 24 | 312 (71.9%) | 201 (70.5%) | 111 (74.5%) | -4.0 | 0.071(-10.8%) | >0.999(-12.7%) |

<u>Composite Endpoint Requested by FDA</u>
FDA requested after the PMA submission that the sponsor define a composite endpoint (entitled the subject performance composite): improvement in weight-bearing pain (≥20 mm on 100 mm VAS); absence of secondary procedures; improvement in function (≥10 point reduction in Foot Function Index); absence of significant graft harvest site pain (<20 mm on 100 mm VAS); and absence of a SAE.  The sponsor also generated a second composite endpoint, consisting of the components of the subject performance composite in addition to the original radiographic endpoint (≥50% osseous bone bridging at 24 weeks).

**Table 33 – FDA Requested Composite End-Point at 24 weeks**

| | Percentage of subjects classified as therapeutic successes at 24 week | | | | |
|---|---|---|---|---|---|
| **Outcome** | **Augment** | **Autograft** | **Difference (Augment – Autograft)** | **1-sided 95% lower bound** | **Non-inferiority *p*-value** |
| **Subject performance composite (SPC)** | 50.0% (130/260) | 47.4% (65/137) | 2.60% | -6.10% | 0.009 |
| **SPC + radiographic** | 34.6% (90/260) | 31.4% (43/137) | 3.20% | -4.90% | 0.004 |

The sponsor concludes that, although the additional components decrease the success rates based on CT scan alone, the relative difference between the two treatment groups is similar; thus, the data continues to support non-inferiority.

Quality-of-Life Assessments
Quality-of-life was assessed using the SF-12 (PCS component), Foot Function Index (FFI), and AOFAS Ankle-Hindfoot questionnaires. Questionnaires were completed prior to treatment, and at 6, 12, 16, 24, 36, and 52 weeks, post-operatively. Success in each category was defined as maintenance or improvement in status post-operatively as compared to the pre-operative condition.

The medical outcomes 12 item Short Form Health Survey (SF-12) was used to assess the general health status of all study patients. Only the physical health summary (PCS) component was utilized and was reported as a "Compound Score". The mean improvement in PCS from pre-op to 24 weeks after surgery for the investigational group was 8.9 (31.0 pre-operative to 39.9 post-operative), compared to 9.8 for the control group (31.6 pre-operative to 41.4). The difference in means supports non-inferiority for the SF-12 PCS in the mITT and ITT populations ($p<0.001$ for both populations).

The Foot Function Index is a self-administered index questionnaire consisting of 23 items divided into 3 sub-scales, providing both total and sub-scale scores. It measures the impact of foot pathology on function in terms of pain, disability and activity restriction. Augment patients showed a mean total score of 27.4 (improvement from 51.6 at screening), compared with 22.3 in the Control group (improvement from 48.6 at screening). The difference in means supports non-inferiority for the FFI total score in the mITT ($p$=0.012) and in the ITT population ($p$=0.011).

The AOFAS Ankle-Hindfoot is a clinician administered index questionnaire consisting of a 100 point scale with 3 sub-groups, and specific to hindfoot and ankle surgical outcomes. It measures the impact of foot pathology in terms of pain, function and alignment. The mean AOFAS Ankle-Hindfoot total for Augment patients was 73.9 (improvement from 44.3 at screening), compared to 75.9 in the Control group (improvement from 44.5 at screening). The difference in means supports non-inferiority for the SF-12 PCS in the mITT and ITT populations ($p$<0.001 for both populations).

The results are summarized in Table 34 below

**Table 34- Quality of Life Assessments**

| Quality-of-Life Outcomes at 24 weeks | Augment (Mean Post-operative Score) | Autologous bone graft (Mean Post-operative Score) | *p*-value |
|---|---|---|---|
| **SF-12 (PCS)** | 39.9 | 41.4 | $p$<0.001 |
| **Foot function index** | 27.4 | 22.3 | $p$=0.012 |
| **AOFAS ankle-hindfoot total** | 73.9 | 75.9 | $p$<0.001 |

Pain Assessments
The Visual Analog Scale (VAS, 100 point scale) scores were used to evaluate pain at the fusion site, pain at the graft harvest site (Controls only), and pain upon weight bearing. Questionnaires were completed prior to treatment, and at 6, 9, 12, 16, and 24 weeks, post-operatively. Success in each category was defined as maintenance or improvement in status postoperatively as compared to the pre-operative condition.

For overall fusion site pain, at week 24, the Augment Bone Graft patients reported a mean overall fusion site pain assessment of 18.9 mm (mean improvement of 32.6 from screening), compared with a mean pain assessment of 16.5 mm (mean improvement 33.0) in the Control patients. These results demonstrated statistical significance for non-inferiority for both fusion site pain assessments (p=0.001).

For pain upon weight bearing, a mean assessment of 23.5 mm for the Augment group was obtained (mean improvement of 43.4 from screening), compared with 19.3 mm for the Control group (mean improvement of 45.4 from screening). The data for the weight bearing pain assessments also support non-inferiority for the mITT population (p=0.016) and the ITT population (p=0.009).

Pain at the bone graft harvest site was recorded only for Control patients treated with autologous bone graft. At week 24, the mean graft harvest site pain assessment was 8.1. Also at week 24 in the mITT population, the percentage of Control patients that reported graft harvest site pain of ≥20 mm was 24.1% at week 12, 14.6% at week 16, and 12.4%. Table 35 (shown below) and Table 36 summarize these results from the graft harvest site.

A summation table for all pain results is provided in table 35 below.

**Table 35- Pain Assessments**

| Pain Assessment Outcomes at 24 weeks | Augment | Autologous bone graft | *p*-value |
|---|---|---|---|
| **VAS pain at fusion site** | 18.9 | 16.5 | 0.001 |
| **VAS pain at weight-bearing** | 23.5 | 19.3 | 0.016 |
| **VAS pain at graft harvest site** | 0** | 8.1 | -- |

One of the proposed clinical advantages of Augment over Autograft is that the Augment device does not require a second surgical procedure at another site to harvest autologous bone graft material. This could theoretically be associated with a lowered incidence of infection, as well as eliminating the potential for graft harvest site pain. To assess this issue, the sponsor assessed graft harvest pain over time using a 100 mm visual analog scale (VAS); the mean VAS score is presented in the table and figure below.

As can be seen, while the majority of Autograft subjects did not report graft harvest site pain of at least 20 mm, a minority did experience pain of 20 mm or greater over an extended period of time. As a result of this, the VAS pain scores are skewed, and thus the mean score may not be representative of the typical Autograft subject’s experience because of the sensitivity of the sample mean to outlying large observations. Therefore, the median VAS pain score is also presented for context, as the sample median does not share this sensitivity to outlying observations.

| Table 36 - VAS pain at graft harvest site over time (Autograft subjects only) | | | | |
|---|---|---|---|---|
| Visit | N | Percent of subjects with significant* pain | Mean | Median |
| Surgery | 119 | | 30.2 | 16 |
| Day 7-21 | 144 | 35.8% | 17.9 | 10 |
| Week 6 | 144 | 19.0% | 10.1 | 2 |
| Week 9 | 134 | 21.9% | 12.8 | 2 |
| Week 12 | 139 | 24.1% | 11.6 | 2 |
| Week 16 | 141 | 14.6% | 9.9 | 1 |
| Week 24 | 143 | 12.4% | 7.9** | 1 |
| Week 36 | 138 | 7.3% | 5.8 | 1 |
| Week 52 | 142 | 8.8% | 5.9** | 0 |

*Subjects reporting graft site harvest pain of at least 20 mm on VAS
***p*-values<0.001 for both non-inferiority and superiority of Augment relative to Autograft at both time-points.

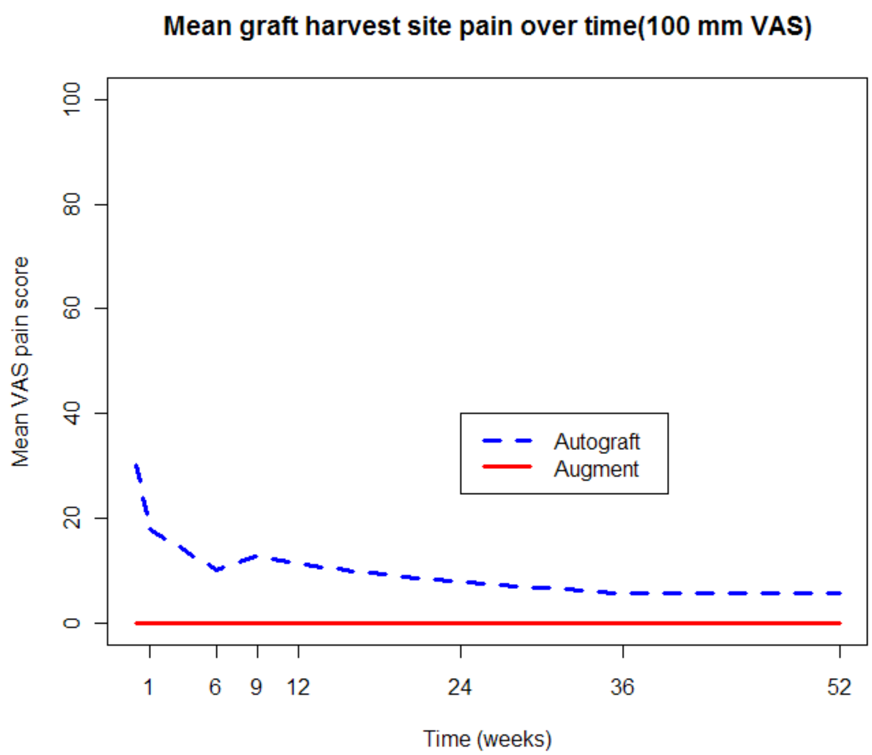


**Figure 4- Donor Site Mean VAS Pain Over Time**

Time-to-Event Analyses
The sponsor's pre-specified time-to-event analyses utilized the Kaplan-Meier (K-M) method for estimation, with the Wilcoxon-Gehan test for hypothesis testing. The main difference between the commonly encountered log-rank test and the Wilcoxon-Gehan test is the relative weighting of the two: the log-rank test weights all time-points equally, while the Wilcoxon-Gehan test weights time-points relative to the risk set (the number of subjects remaining in the dataset at that time who have not yet experienced the event or been censored). Thus, the Wilcoxon-Gehan test weights earlier time-points more heavily due to there being more subjects in the risk set earlier on.

Four time-to-event analyses were conducted: time to fusion by CT, time to radiographic healing, time to clinical union, and time to no pain on weight-bearing. There were no significant differences between the two treatment groups for any of these time-to-event outcomes ($p>0.05$ for all).

**Clinical Study Discussion**

The Augment rh-PDGF-BB device is intended for patients over the age of 18 years requiring a hindfoot/ankle fusion involving a bone grafting procedure. It is to be used as an alternative bone grafting substitute to autologous bone graft that requires an invasive harvest procedure. The clinical data provided in this application relates to short and mid-term safety and effectiveness data for the subject device.

Long-term data, although not intended as the primary outcome measure of success, suggests however a less favorable profile. The number of patients with high titer antibody results and the uncertain results of the neutralizing assay raise potential concerns. Recombinant PDGF-BB has systemic effects, not unlike any other drug, and the medical community does not have enough information that relates to its long term pharmacological effects for this specific intended use.

The PMA includes data from 272 investigational and 142 control patients treated in the multicenter (38 sites), prospective, controlled clinical investigation of the AUGMENT™ device as compared to autogenous bone graft. All patients have reached the 24-week follow-up visit, the primary endpoint. The primary effectiveness endpoint of the trial was CT fusion rate provided by the sponsor as an analysis of a full complement of joints in a modified intent to treat population (mITT). At week 24, 61.2% of Augment patients were deemed successful by CT scan with 50% osseous bridging, compared with 62.0% of patients treated with autologous bone graft. The investigational group was found to be statistically non-inferior to the control group in the mITT population ($p=0.038$), but not in the ITT population ($p=0.065$). As is noted above, sponsor's original IDE plan proposed to evaluate an intent to treat (ITT) population for success.

Data from the IDE clinical trial demonstrate that the clinical results for the AUGMENT™ group were statistically non-inferior to the control group in terms of overall success for the primary endpoint, secondary patient outcome measures of pain and function, and adverse event rates.

However, superiority was not established and the overall fusion rate for both groups (60 to 65%) at 24 weeks is low. For other time points, most notable those beyond the 24 weeks, the device fails to find statistical non-inferiority to the control group. Moreover, in assessing the overall success of the primary endpoint, all adverse events, all secondary surgeries, and analyses of function were not considered, except by post-hoc analysis

The sponsor notes that the adverse event rates of Augment device were comparable to those in the control treatment utilizing their current method of categorizations, with the exception of graft site related adverse events, in which there was a difference. The investigational group did not undergo graft site harvesting. However, it is unclear if the sponsor's categorizations of adverse event are adequate or complete.

With regards to safety, a higher incidence of investigational patients developed neoplastic events when compared to controls (5I (1.8%) versus 2C (1.4%)). In the investigational group, 3 of the 5 neoplasm events were considered as high grade, high morbidity metastatic cancers of the prostate (2) and breast, with all 3 either present or suspected clinically prior to receiving the investigational device and prior to biopsy proven cancer diagnoses. These findings are potentially concerning given the history of the Regranex product and the association with pre-existing cancers. Moreover, the IDE protocol did not have an exclusion criterion for pre-existing cancers, but only for those untreated malignant neoplasms at the surgical site, or those patients currently undergoing radio-or chemotherapy. Because this information would be biased in retrospective assessment, a post-approval study designed for adherence to cancer pre-screening and exclusion of any pre-existing cancer should be done. FDA would like to get the Panel to weigh in on the need for additional pre-market or pre-clinical studies of the cancer risk versus any potential benefit of the device.

The formation of anti-PDGF-BB antibodies during the course of the 24 week study demonstrated that this particular combination and dose of PDGF-BB, as a device, has created an immunostimulatory antigen. At least two patients had measurable levels of antibody present for a year or more. The magnitude and duration of the antibody response cannot be interpreted in the current data set, especially as it relates to such clinical concerns as pregnancy and autoimmunity. FDA is not sure how labelling could address these concerns based on current data in the PMA.

The investigational group does not appear to be effective (or non-inferior) for the primary endpoint of "full complement" evaluation at 50 and 75% osseous bridging for any time-point except the primary endpoint of 24 weeks in both the ITT and mITT groups. The clinical indications for surgery were not clear, as patients were enrolled that required fusions of both the ankle and hindfoot. Although "full complement of joints" would provide an indication for the package insert, the current data set is potentially uninterpretable as to what patient population would clinically benefit from the use of this device.

To summarize, FDA has the following concerns:

1. The intended patient population. Because of the heterogenous nature of patient enrollment for both ankle and hindfoot fusions, it is not clear who would be clinically indicated for the device's use. The heterogeneity of the patient population studied also confounds the assessment of success and failure as it relates to adverse events and secondary surgeries seen more often in the investigational group. Moreover, any potential benefit appears from the available data - to be of a limited time course, while there may be long-term risks of cancer, immunological, and/or other adverse events.
2. The data provided for the primary endpoint is based on fusion as assessed by CT measures alone that directly impacts the risk/benefit assessment for this device. This evaluation of the primary endpoint of fusion raises issues of valid clinical efficacy, in part because:

   a. The radiographic method of analysis is possibly "novel" and has not been externally validated.
   b. The sponsor did not provide a literature review that assesses by radiographs what is a clinically acceptable fusion rate for this patient population.
   c. The composite endpoint did not study weight bearing and other pain priori (as FDA recommends in current studies for consideration for pre-market applications).
   d. The primary endpoint also did not measure clinical function or clinical improvement of the involved joint.
3. The immunostimulatory nature of the device. Safety concerns related to the long term effects of anti-PDGF-BB antibodies in pregnancy and their potential implications in autoimmunity.
4. The issue of reoperations and how they relate to the device's failure cannot be assessed using the current data. Moreover, there are other potential issues with adverse event reporting and interpretation that may make an evaluation of the safety, efficacy, and benefit of the device not delineated with the current data set. FDA and the DSMB have independently raised related issues in this regard to the sponsor.
5. The sponsor is claiming a benefit of avoiding ICBG by use of their device. ICBG was a small percentage of the source material used in the controls. The majority of autologous grafting was from areas historically associated with low morbidity and pain. The potential benefits, "trade offs" and risks (especially the fully unanswered question of its toxicology potential, especially in regards to cancer association) of this device vs. ICBG do not seem to be fully answered by the current data.
6. The ability to determine the true clinical success is confounded by the use of clinical outcome instruments, which are not based on categories widely accepted in the literature as clinically meaningful differences between treatment groups; but rather a numerical and/or summation of changes intra-comparatively between preoperative and postoperative scores.

In stating the above concerns, FDA recognizes that the sponsor has shown potentially a marginally non-inferior study (albeit if the panel agrees with the use of mITT vs. the ITT). However, FDA still has clinical concerns with the safety and overall risk/benefit of the device at this time, primarily due to the unanswered question of safety in regards to the potential for cancer formation versus an unproven benefit in the current standard for care.

## POST APPROVAL STUDY

**NOTE TO PANELISTS:** FDA's inclusion of a section/discussion on a post-approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are FDA's comments regarding potential post-approval studies. The sponsor has submitted a brief study plan for a possible post-approval study to assess the long term effectiveness and safety post implantation of Augment™ Bone Graft. The sponsor has proposed a prospective study to evaluate the effectiveness and safety at year 5 post-implantation.

**Objective**

The sponsor's stated objective for the proposed post-approval study is to assess the long term safety of Augment Bone Graft (0.3 mg/ml rh-PDGF-BB/β-TCP) in its potential to provide equivalent outcomes to autologous bone graft (ABG) in hindfoot and ankle fusion models, without the need for additional surgery to harvest bone graft. No specific study hypotheses are described.

**Enrollment and Follow-up**

A maximum of 397 among the 414 study subjects treated under IDE protocol BMTI-2006-01 will be consented and requested to return for long-term follow-up (up to 60 months) as part of a post approval study. Patients will be followed at 36 months (±3 months), 48 months (±3 months), and 60 months (±4 months). Only the 36-month visit is a clinical visit, at which time, patients are consented to for the extension study. All other visits are telephone screens. Patients will be contacted in the interim to optimize follow-up and future compliance.

**Outcomes**

Effectiveness
Not described.

Safety
Including neoplasms, deaths, and SAEs related to the following SOCs:

- Infections and infestations (LLT of cellulitis, wound infection, post-operative wound infection);
- Musculoskeletal and connective tissue disorders (pain in ankle/joint, swelling in ankle/joint, arthralgia associated with the surgical foot/ankle);
- Neoplasms benign, malignant and unspecified (including cysts and polyps) (all lower level terms associated with neoplasms)
- Complications related to bone graft harvest

Endpoints of effectiveness are not provided.

**Statistical Plan**

Sample Size Calculation
Sample size calculation is not provided. A maximum of 397 patients is available for the PAS. This sample size is not determined by study hypothesis.

Analysis
The sponsor proposes to use "descriptive statistics comparing long term safety of Augment to autograft." No additional details are provided.

**FDA Comments on Proposed Post-Approval Study**

*1. Study Hypothesis*
The proposed study is not hypothesis driven. A study hypothesis is needed to evaluate whether the study is designed properly to address the study objectives.

*2. Enrollment and follow-up*

The sponsor proposes to follow patients enrolled in the IDE study up to 5 years post-implantation. The proposed study may lack of generalizability to a broader patient population in the real world.

a. The IDE study included sites with experience in clinical studies and investigational devices. The generalizability of these safety and effectiveness results to less experienced facilities and operators is concerning
b. The study plan does not present a goal of the follow-up rates over time. The sponsor did not describe measures to control patient loss-to-follow-up over the study period.
c. The study plan does not evaluate the study power or accuracy for the safety endpoints.
d. It is not clear how the follow-up time of 5 years is determined.
e. The rationale of the clinical follow-up visit at only 36 months is not described.

*3. Outcomes and endpoints:*

The sponsor proposal only includes a list of safety endpoints, but there is no hypothesis associated with the listed endpoints. Additionally, there is no plan to collect long-term effectiveness data.

The FDA will be asking a question regarding post approval study or studies if the product was deemed approvable by FDA.